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Cardiovascular Risk Factors in Rheumatoid Arthritis

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of MD

by

Dr Firdaus Fatima

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Declaration

I declare that this thesis entitled:

Cardiovascular Risk Factors in Rheumatoid Arthritis

is entirely my own work and that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

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Dedication

This work is dedicated to:

My father Prof. Mirza Akbar Ali Baig - the way you lived your life has always been an inspiration for me.

My husband Ashraf Hadi - your emotional support and companionship will always be missed.

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Abstract

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with unknown aetiology. The prevalence of RA in South Asian Indians is 0.75%. Compared to the general population; RA patients have a reduced life span which is mostly due to cardiovascular disease (CVD). The increased risk of CVD, observed in RA, may be due to a combination of RA disease activity, medicines used to treat RA and traditional cardiovascular (CV) risk factors. Much of the published work exploring these associations has been conducted in North American and European RA cohorts. South Asian Indians are known to have an increased prevalence of traditional CV risk factors and metabolic syndrome as well as premature CVD events compared to Caucasians. It is not known, in South Asian Indian patients, whether having RA increases this CV risk further. In addition influence of increased RA disease activity and treatment on CV risk in Indian RA patients is not well studied.

Aims

The aim of this thesis is to measure the prevalence of traditional risk factors for CVD in urban Indian patients with (RA) and to compare these risk factors with age and gender matched normal controls from similar geographic location. The effect of treatment by biologic disease modifying anti rheumatoid drug (DMARD), etanercept and newer traditional DMARD leflunomide on traditional CV risk factors are also studied.

Methods

Consecutive South Asian Indian RA patients attending a rheumatology clinic in the city of Hyderabad, India, who fulfilled 1987 ACR criteria, were included in this study. Age and gender matched controls from the same geographic location were recruited. Traditional CV risk factors were measured and composite coronary heart disease (CHD) risk scores for the probability of a CHD event in next ten years were calculated. Metabolic syndrome criteria were applied to all participants. Prevalence of CV risk factors was explored in the RA patients. Prevalence of CV risk in RA cases was compared to that in the control group using logistic regression adjusting for age and gender. Within the RA cohort, associations between disease activity and measures of CV risk were explored. In addition, the influence of initiating drug therapy with leflunomide and etanercept on CV risk was evaluated in small subgroup analyses.

Results

Eight hundred RA patients and 800 controls were recruited. RA patients had increased prevalence of almost all the traditional CV risk factors. The cases and controls displayed increased prevalence of increased BMI. Co morbidities were more frequently observed in RA cases and RA was associated with increased prevalence of diastolic hypertension, elevated fasting blood glucose, high waist hip ratio, elevated total cholesterol and a trend for lower HDL cholesterol. Almost half of the cases fulfilled

criteria for metabolic syndrome. RA patients had a four times increased odds of having elevated CHD risk scores when compared to controls.

RA disease activity was not associated with traditional CV risk factors. Leflunomide did not cause hypertension; interestingly the patients with pre treatment elevated systolic BP had a reduction in BP after treatment with leflunomide. There was a modest improvement in atherogenic index. No significant change in metabolic syndrome was observed. A short course of etanercept treatment did not have a sustained effect on CV risk factors. It was encouraging to notice a sustained reduction in disease activity even after etanercept therapy was withdrawn.

Conclusions

South Asian Indian patients with RA have a very high prevalence of traditional CV risk factors despite their young age and predominantly female population. In particular, marked elevation in CV risk factors associated with the metabolic syndrome were observed in RA patients compared to population controls. This increased prevalence of CV risk does not appear to be associated with high RA disease activity. The effect of treatment to reduce disease activity has not demonstrated significant changes in CV risk factor profiles in patients with RA. As the background rate of CVD events is high in this population, the RA patient appears to be at greatly increased risk. Targeting CV risk factor reduction in these patients may substantially reduce CV event rates in RA.

Presentations

Oral

- Suppression of Rheumatoid Arthritis Disease Activity Using 3 Months of Etanercept Treatment Does Not Significantly Modify Traditional CVD Risk Factors. Firdaus Fatima, URK Rao, R J Moots, N J Goodson. International Journal of Rheumatic Diseases 2008; 11S1:120
- Benefit of Short Course of Etanercept in Patients with Active Rheumatoid Arthritis with Sub optimal Response to Traditional DMARDs. URK Rao, Firdaus Fatima, Satyavati C, Sivanand J, Datta Kumar. International Journal of Rheumatic Diseases 2008; 11S1: 408.

Poster

- Prevalence of cardiovascular risk factors in elderly patients with rheumatoid arthritis. Firdaus Fatima, U R K Rao, R J Moots, N J Goodson – Indian Journal of Rheumatology 2008;3S1:28.
- Prevalence of Cardiovascular risks in Rheumatoid Arthritis. Firdaus Fatima, U R K Rao, R J Moots, N J Goodson - APLAR Journal of Rheumatology 2006; 9 S1: A389.
- Prevalence of cardiovascular Risk Factors in Patients with Rheumatoid Arthritis: Results from a South Asian population. Firdaus Fatima, U R K Rao, R J Moots, N J Goodson – 2007 Arthritis Rheum 2007;58 S:1014
- Raised Traditional Cardiovascular Risk Factors in Indians with Rheumatoid Arthritis. Firdaus Fatima, Uppuluri RK Rao, Robert J Moots, Nicola J Goodson. Arthritis Rheum 2009; 60 S: 948.
- High Rheumatoid Disease Activity Is Associated With Lower Triglyceride Levels: A study of Indian patients with Rheumatoid Arthritis. Firdaus Fatima, U R K Rao, R J Moots, N J Goodson. Rheumatology 2010;49S I:151
- Prevalence of Co Morbid conditions in patients with rheumatoid arthritis: case control study. Firdaus Fatima, RK Rao Uppuluri, Robert J Moots, Nicola J Goodson International Journal of Rheumatic Diseases 2010; 13 S1:349.

Abreviations

Ab	Antibody
Anti CCP	Anti cyclic citrulinated peptide
ACR	American college of rheumatology
APLAR	Asia Pacific league against rheumatism
ARA	American rheumatology association
BHS	British hypertension society
BMI	Body mass index
BP	Blood pressure
CADI	Coronary artery disease in Indians
CVA	Cerebro vascular accident
CI	Confidence interval
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
CRP	C reactive protein
CIMT	Carotid intima media thickness
DAS	Disease activity score
DMARDs	Disease modifying anti rheumatoid drugs
DHEAS	Dehydro epiandrosterone sulphate
ELISA	Enzyme linked immuno sorbent assay
EULAR	European league against rheumatism
ESR	Erythrocyte sedimentation rate
Fc	Fragment crystalline
FF	Firdaus Fatima
HCQS	Hydroxychloroquine
HRT	Hormone replacement therapy
HAQ	Health assessment questionnaire
HTN	Hypertension

HDL-Chol	High density lipoprotein cholesterol
HLA	Human leucocytic antigen
IHD	Ischeamic heart disease
IDF	International diabetes forum
IRA	Indian rheumatology association
IQR	Inter quartile range
JBS	Joint British societies
LDL-Chol	Low density lipoprotein cholesterol
MHC	Major histocompatibility complex
MIF	Macrophage inhibiting factor
MS	Metabolic syndrome
Mtx	Methotrexate
n	Number
NCEP ATP	National cholesterol education programme adult treatment panel
NSAIDs	Non steroidal anti inflammatory drugs
OA	Osteoarthritis
OR	Odds ratio
OLIG 3	Oligodendrocyte lineage transcription factor 3
PAD14	Peptidyl arginine deiminase, type 4
PTPN	Protein tyrosine phosphatase non-receptor
RF	Rheumatoid factor
SE	Shared epitope
STAT	Signal transducer and activator transcription
SLE	Systemic lupus erythematosis
T Chol	Total cholesterol
TG	Triglyceride
TNF	Tumor necrosis factor
T2DM	Type 2 diabetes mellitus
URKR	Uppuluri Ramakrishna Rao
WHO	World health organisation

Chapter 1 – Introduction

1.1 Background

Rheumatoid arthritis (RA) is a chronic, systemic, immuno inflammatory disease of unknown aetiology. The term Rheumatoid arthritis was coined by Garrod in 1859 (Garrod, 1859).

RA is characterized by bilateral symmetrical polyarthritis with a chronic fluctuating course, resulting in disability due to progressive joint destruction and deformity. The clinical features are articular and extra-articular. Extra articular features are given in Table 1.1

Table 1.1 Extra articular manifestations seen in rheumatoid arthritis

General and systemic features Anaemia, fever, fatigue, weight loss, cachexia, Rheumatoid nodules Vasculitis Raynauds phenomena Secondary sjogrens syndrome Feltys syndrome
Organ involvement Eye - scleritis, episcleritis, kerato conjunctivitis Lung - pleuritis, interstitial lung disease Kidney - Glomerulonephritis, amyloidosis Neuromuscular – neuropathy,neuritis, myopathy Cardiovascular – pericarditis, endocarditis, atherosclerosis, coronary artery disease, stroke

1.2 Diagnosis of RA

Diagnosis of RA is mainly clinical as there is no definite diagnostic test. In patients with a short history of joint pain, the diagnosis can often be difficult.

1.2.1 Rheumatoid Factor

Rheumatoid factors (RF) are autoantibodies (Ab) against Fc (fragment crystallisable) portion of IgG. The RF can be detected by latex agglutination, enzyme linked immuno assay (ELISA) or nephlometry. Latex agglutination method is routinely used in clinical practice. RF is positive in 70 – 80 % of patients with RA (Masi et al., 1976). Twenty to thirty percent of patients with established disease may be negative for RF; this group of patients are classified as having RF negative arthritis which has a relatively mild course and better prognosis. RF has limited specificity and can be present in rheumatic conditions other than RA like systemic lupus erythematosus (SLE), acute and chronic infections and neoplasms, in these conditions the RF is nonspecific, of IgM type and of low affinity (Martinus AM van Boekel, 2002). RF is positive in 5% of general population and the prevalence increases with increasing age. Some studies have demonstrated that the prevalence of rheumatoid factor decreases after the age of seventy years (Gran et al., 1984). The presence of RF in high titres is associated with severe erosive arthritis and presence of extra articular features (Scott, 2000, Lindqvist et al., 2005). Features present at disease onset which have a correlation with better disease outcome are: negative for rheumatoid factor, less involvement of upper limb joints, acute onset of arthritis below the age of thirty years and male gender (Masi et al., 1976).

1.2.2 Anti CCP

Anti cyclic citrullinated peptide (anti CCP) antibodies against citrullinated residues of protein are found in the serum of RA patients. These antibodies were defined in 1998. Like RF they have a sensitivity of 70% but their specificity is up to 95% (Schellekens et al., 1998). This test is useful in individuals who test positive for RF due to infection or as part of the normal population variation. More than 30% of patients with RF-negative arthritis are positive for anti CCP antibodies, these are better indicators of erosive RA but do not predict extra articular disease (Rantapaa-Dahlqvist S, 2003). Patients with positive RF and anti CCP Ab have a strong possibility of radiographic erosions (Meyer O, 2003). Indian patients with RA demonstrate anti-CCP antibodies in 80% of established RA and predict erosive disease in RF positive and RF negative individuals (Shankar et al., 2006).

1.3 ACR classification Criteria

The first criteria to aid classification of RA were published (Ropes et al., 1958) by a committee of the American Rheumatology Association (ARA; 1956) that were widely used for the next thirty years. Later, the American College of Rheumatology (ACR) revised the criteria in 1987 for classification of RA and not for diagnosis (Table 1.2). The criteria are helpful in classification of RA and have a sensitivity of 94% and a specificity of 89% (MacGregor, 1995). They are widely used in epidemiology studies and clinical trials. However, it is difficult to identify early RA using these criteria because two out of the seven criteria (subcutaneous nodules and radiographic erosions) are frequently not present in early disease. At least four of the criteria listed below must

be fulfilled to classify a patient as RA. The ACR criteria have been developed for Caucasian patients but are found useful to all populations. However, there are no studies reporting validity of the ACR criteria for Indian populations.

Table 1.2 The 1987 ACR classification criteria for rheumatoid arthritis (Arnett et al., 1988)

Criterion	Comment
1. Morning stiffness	Duration > 1 hour lasting > 6 weeks
2. Arthritis of at least three areas	Soft tissue swelling or exudation lasting > 6 weeks
3. Arthritis of hand joints	Wrist, metacarpophalangeal (MCP) joints or proximal interphalangeal(PIP) joints lasting > 6 weeks At least one area lasting > 6 weeks
4. Symmetrical arthritis	As observed by a physician
5. Rheumatoid nodules	As assessed by a method positive in less than 5% of control subjects
6. Serum rheumatoid factor	
7. Radiographic changes	As seen on anteroposterior films of wrists and hands

The ACR criteria have been used widely over past two decades. Recently, another revision of the classification criteria for RA has been undertaken. These new criteria were jointly developed by the ACR and EULAR (European League Against Rheumatism) (Aletaha, 2010).

1.4 Epidemiology of Rheumatoid Arthritis

1.4.1 General incidence and prevalence

Rheumatoid arthritis is prevalent all over the world covering all ethnic groups. Based on the classification criteria several studies have observed a worldwide prevalence of 0.5 – 1% in adult population. Studies have shown that geography, climate, (Spector, T.D.1995) genetics and environment play a role in the development of RA. Onset of disease is between fourth and sixth decade of life and the incidence increases with increasing age.

Table 1.3 Prevalence of rheumatoid arthritis

Population	Size	Prevalence (%)	Reference
South Africa			
Rural	801	0	(Beighton et al., 1975)
Urban	964	0.9	(Solomon L, 1975)
Nigeria	2000	0	(Silman et al., 1993)
Europe and N America			
UK	2234	1.1	(Lawrence, 1961)
US Adults	6672	1	(Engel 1968)
US Whites	4552	0.9	(Cathcart and O'Sullivan, 1970)
National Sample, Denmark	19,100	0.8	(Sorenson, 1973)
Heinola, Finland	8,000	2	(Aho et al., 1989)
Hanover, Germany	11,534	0.5	(Mau, 1991)
Belgrade, Serbia	2184	0.2	(Stojanovic et al., 1998)
Holland, Sweden	3928	0.5	(Simonsson et al., 1999)
Brittany, France	2740	0.6	(Saraux et al., 1999)
Norfolk, UK	6593	0.8	(Symmons et al., 2002)
Madrid, Spain	2998	0.5	(Carmona et al., 2002)
Izmir, Turkey	2887	0.5	(Akar, 2006)
Native American			
Inuit, Eskimos, Canada	2055	1.8	(Oen et al., 1986)
Southeast, Alaskan, Indians	5169	2.4	(Boyer et al., 1991)
Pima Indians, USA	2895	2	(Jacobsson et al., 1994)
Inupiat, Alaska	1651	1.4	(Boyer et al., 1998)
Yupik, Alaska	2135	0.6	

In a prospective population study in Norfolk, United Kingdom, Symmons et al (1994) observed an incidence of 3.4 in women and 1.4 in men per 10,000 subjects that corresponds to a threefold increased prevalence observed in women. The gender difference in prevalence becomes narrower as age advances. Many prevalence studies have also been conducted in American, Asian and African populations as given in Table 1.3

1.4.2 Prevalence in Asia

The prevalence of rheumatoid arthritis varies due to changes in geographic location, ethnic groups, methods of survey, definition of the disease and the classification criteria used. The overall prevalence of RA in Asians is less than that seen in Caucasians (Table 1.4). There is difference in the occurrence of RA in rural and urban areas (Chou et al., 1994). There is trend for rheumatological complains to be more frequent in urban areas the reasons are not known and their differentiation into type of disorder was not done (Das, 2005). However, a study in Indians from Pune has reported RA to be more common in rural populations (Chopra, 2009).

The mean prevalence in Asia is about 0.3 with an exception of Middle Eastern countries where it is higher. It is proposed that this difference may be due to variations in genetic, environmental and socio-economic factors, like social class (affluent and poor), level of education, type of work (manual labourers) described later (Section 1.5.3.3).

A comparative study between British and Malaysian patients concluded that, whilst the disease activity and functional disability were similar, differences existed in pattern of

disease and distribution of joint involvement (Veerapen, 1992). The British patients had more severe involvement of feet and had extra articular manifestations whereas in the Malaysian patients wrist and cervical spine were more commonly affected and sicca syndrome was common. There is not much published literature regarding difference in RA patients from countries in Asia.

Table 1.4 Epidemiology of rheumatoid arthritis in Asia, Middle East and Far East

Population	Size	Prevalence (%)	Reference
Japan –Kamitonda	2276	0.3	(Shichikawa et al., 1981)
China			
Kinmet	5629	0.3	(Beasley et al., 1983)
Shanghai	7603	0.3	(Dai et al., 2003)
Hong Kong- Urban	2002	0.3	(Lau et al., 1993)
Taiwan - Rural	3000	0.3	(Chou et al., 1994)
Urban	6000	0.9	
Indonesia - Java	4683	0.2	(Darmawan et al., 1993)
India - Rural	39826	0.75	(Malaviya et al., 1993)
India Pune Urban	4092	0.3	(Chopra, 2009)
Rural		0.6	
Pakistan - Urban	2090	0.55	(Farooqi and Gibson,
Malaysia Rural	2594	0.15	1998)
Vietnam – Urban	2119	0.3	(Veerapen, 1992)
Iraq	6999	1	(Minh Hoa et al., 2003)
Oman	1925	0.8	(Al-Rawi et al., 1978)
			(Pountain, 1991))

1.4.3 Epidemiology of rheumatoid arthritis in India

Prevalence of RA amongst the Indian adult population that forms the basis of this study is in the range of 0.2- 0.75% which is less than that described in Caucasian cohorts (Malaviya et al., 1993, Chopra A, 2001, Das SK, 2004) but relatively higher than other Asian countries. In comparison, the natural history of the disease is similar to Caucasians but with some differences. The disease onset is earlier – between third and fifth decade (Chandrasekharan AN, 1994), course of the disease is milder, involvement

of the wrist joint and the forefoot is reduced . Extra articular features are less frequent and less severe (Chandrasekharan AN, 1994). Rates of RF positive RA are lower than in Caucasians. HLA DR 4 may not correlate well with RF positive and severe disease (Chandrasekharan AN, 1994). RA has a polyarticular onset, the disease activity is milder but severe crippling disease is also seen.

Differences are observed in the disease characteristics in North and South India. In South Indians RA has a predilection for involvement of PIP joints whereas involvement of wrist joint is seen in North Indians. Hip joint is less affected in South Indians. Knee joint involvement is common in both the regions. Forefoot is less commonly affected and subtalar arthritis is common in both Asians and Indians. The extra articular features are uncommon and less severe, isolated eye involvement in the form of episcleritis is seen. Sicca syndrome is more prevalent in Asians and North Indians when compared to South Indians and Caucasians (Malaviya et al., 1983, Smith CR, 1993, Veerapen, 1992, Veerapen et al., 1993, Chandrasekharan AN, 1994).

A cohort of 400 RA patients attending a hospital in Mumbai (formerly Bombay) in western India was studied. The median age of onset of RA was thirty six years and 88% were females. Majority of the patients were educated, married and were found to be non-smokers. At the onset of arthritis 39% of the females were postmenopausal and the age at menopause was found to be 45.7 years. Smoking history was observed in 4% of individuals. Onset of RA in post partum period was observed in 1% of the cohort. History of tuberculosis and hepatitis in the past was reported by 11.5% and 13% of the

participants. Positive family history of RA was reported by 10%. Majority of the participants reported a history of using alternate therapy in the past and one fourth of them were already taking GCS at the time of presentation to the rheumatologist. It was also observed that the 15% of patients had extra articular features in the form of anaemia, rheumatoid nodules, vasculitis or episcleritis (Kundu AK, 2004).

According to a survey conducted in North India looking at the prevalence of RA in a rural population that comprised mainly manual labourers, RA was found at a prevalence of 0.75%. Close to 40,000 individuals were screened and about 3,400 persons had symptoms suggestive of RA but only 0.75% (299) fulfilled ACR criteria. The male to female ratio was found to be 1: 9.3 and maximum cases were observed in the age group 25 – 29 years. The number of non-responders to survey questionnaire was 10.5% (Malaviya et al., 1993). Urban Indians (west region) in Pune demonstrated 0.2% prevalence of RA which is lower than the rural population (0.5%) (Chopra, 2009). In another study of 213 RA patients, average age 37 years the incidence was maximum in second and third decade followed by fourth and fifth decade. Less than 1% of the patients had a disease onset after 60 years. It was noted that RA in Indians is more aggressive at onset (Akerkar SM 2004). Among rural and urban individuals (North India) it was found that rheumatological complaints were more common in individuals from urban areas. No differentiation studies of the symptoms into the type of arthritis were undertaken (Das SK, 2004).

1.5 Risk factors associated with the development of rheumatoid arthritis

The exact aetiology of rheumatoid arthritis is unknown. Risk factors implicated so far include genetics, smoking, infectious agents, oral contraceptives and in some instances due to neglect from a possible lack of education. The disease probably develops due to contribution, combination and interaction of these factors. Oliver and Silman (2006) summarized that one third of the susceptibility of RA can be explained by environmental risk factors and RA mostly develops due to gene environment interactions eg smoking and HLADRB1.

1.5.1 Genetics

Rheumatoid arthritis has a genetic predisposition. First-degree relatives of an individual with rheumatoid arthritis have two to four times' higher risk of developing the disease. Studies in monozygotic twins have suggested a concordance rate of 15 - 20 % (Jarvinen and Aho, 1994) whereas the concordance rate in non identical twins is only 4 %. There are many ethnic differences in the genetic susceptibility of RA.

Genetic studies have identified a role of Major Histocompatibility Complex (MHC). Molecular genetic studies (Gregersen et al., 1987) confirm an association between the occurrence of rheumatoid arthritis and polymorphism of genes on chromosome 6 which code for a hyper variable region of the b chain of HLA DR molecules. MHC class II alleles especially HLA DRB1 have the strongest genetic association in RA patients but account for less than 40 % of the genetic contribution to rheumatoid arthritis. Statsny et

al in 1978 observed an association between rheumatoid arthritis and HLA DR4 in Caucasians (Stastny, 1978).

Subtypes of HLADR have been identified – DW4, DW14, DW1, coded by DRB1* 04041, * 0101. These subtypes differ in the primary sequence of amino acids but are similar at positions 70 – 74 in the third hyper variable region of HLA DRB1 chain called the shared epitope (SE) (Gregersen et al., 1987). It is hypothesized that the shared epitope has a positive association with rheumatoid arthritis. HLA DRB1* 04, when present, correlates with RF positive, erosive and extra articular disease. In Indians, the association of DQw7 with RA has been observed whereas other studies have reported a disease association with DQw8, hence the DQ association with HLA DR 4 positive may be race dependent and not related to severity of disease (Taneja et al., 1992).HLA DR 4 subtypes DW 10 and DW 13 coded by * 0402 and * 0403 genes are negatively associated with rheumatoid arthritis.

Studies from Birmingham and Manchester in the United Kingdom have found a strong association of HLA DR 4 with evolution of early disease to definite RA and that shared epitope facilitates persistence or severity of disease (Thomson et al., 1993). Weyand et al from the United States observed a phenotype and dose effect of shared epitope – vasculitis was associated with homozygosity and rheumatoid nodules were associated with heterozygosity for HLA DRB 1 * 0401 (Weyand et al., 1992). Studies from India (Agrawal S, 1995), Spain (Moreno et al., 1996) and Taiwan (Yen et al., 1995) have demonstrated a link of severity with shared epitope. Studies in Asian patients (Chinese,

Malay and Indians) observed an association of RA with DRB1*1001 and DRB1 *0701 may be protective (Kong et al., 2002). In Indians, HLA DR 4 did not correlate well with RF positive and severe disease (Chandrasekaran and Radhakrishna, 1995). But another study demonstrated an association of HLADR 4 and RA. Indians residing in Varanasi (north eastern region) reported an association of HLA class 1 antigen A 2 more than B 40 (Agrawal et al., 1996). Susceptibility to RA is related to DRB1*0401, *0404,*0405,*1001 and *0101 in 60 – 70 % of patients and 25% of studied subjects did not show shared epitope. RA did not have a significant association with HLA-DRB1 in Indian patients from the community and hospital referred from Maharashtra (Chopra A, 2000). On the other hand, researchers from Finland (Mottonen 1988), Switzerland (Seitz et al., 1996), Greece (Boki KA 1993), Sweden (Eberhardt K 1996), Canada (Suarez-Almazor ME 1995) and Australia (Saudan A 1996) were unable to show a relationship between HLA status and disease severity. The shared epitope is hypothesized to contribute in disease pathogenesis by influencing CD4 + T cells and molecular mimicry.

As the HLA genes account for less than 50% of the genetic component in RA, T cell receptor genes may also contribute to the susceptibility of developing RA. Recent studies have demonstrated a controversial role of HLA DR genes in RA and that the shared epitope may not be an independent risk factor for RA but may be a marker for immune reactivity and anti CCP antibody (van der Helm-van Mil et al., 2006). Recently non MHC related susceptibility loci have been identified which include protein tyrosine phosphatase non-receptor 22 (PTPN 22), signal transducer and activator

transcription (STAT) 1 and STAT 4, oligodendrocyte lineage transcription factor 3 (OLIG3) and TNF alpha induced protein 3 (TNFAIP3), cytotoxic T lymphocyte associated antigen (CTLA4), peptidyl arginine deiminase, type 4 (PADI4), Macrophage migration inhibitory factor (MIF).

PTPN 22 gene located on chromosome 1p 13 has shown a linkage with RA and is considered the second largest genetic risk in development of the disease. It has regulatory activity for T and B cells. Studies in Caucasians have confirmed the association of this gene with RA. An association with RA and this gene polymorphism has not been shown in Japanese patients (Ikari et al., 2006).

Recently a gene signal transducer and activator transcription (STAT) 1 and STAT 4 on chromosome 2q has been identified in North American population (Remmers et al., 2007). The effect of this association was found to be weak in a Swedish population with a recent disease onset. Subsequently, a Korean study has confirmed the association (Lee et al., 2007a) with RA. This is the first non-HLA gene that has shown association with RA in two different ethnic populations.

The advent of genome wide association studies has resulted in innumerable single nucleotide polymorphisms (SNP) to be genotyped in many samples. A collaborative work in British population by the Wellcome Trust case control consortium (WTCCC) has studied 1860 RA and 2930 controls and observed two well known RA susceptibility genes HLADRB1 and PTNP22 (2007) (The Wellcome Trust Case Control Consortium

Genome-wide association study). Nine variants were found associated with RA. These variants were studied in a subsequent study by WTCCC in a large case control cohort of UK population and identified a SNP in the intergenic region of 6q23 to be strongly associated with RA and this association was independent of HLADRB1 and PTNP22 genes (Thomson et al., 2007). SNP in gene CD244 is associated with RA in Japanese (Suzuki et al., 2008) but not in other populations. The SNP was linked to two genes - oligodendrocyte lineage transcription factor 3 (OLIG3) and TNF alpha induced protein 3 (TNFAIP3). The same was observed by a study in US population (Plenge et al., 2007b). Another gene identified to be associated with RA is the TRAF1 and C5 this study was done in anti CCP positive RA patients from North America and Sweden (Plenge et al., 2007a). PAD 14 gene studies have shown an association with RA but this was confirmed in only one study in Asian – Japanese population and not in studies in Caucasians. A meta analysis of Asian and European studies (Lee et al., 2007b) has demonstrated that Asians have an association of PAD 14 polymorphism with RA. PAD 14 is the second most important locus after HLA DRB1. There is paucity of published data in genetics of RA in Indian patients.

1.5.2 Hormones

A greater incidence of RA among pre menopausal females suggests an influence of reproductive and hormonal factors. Hormonal risk factors exert their effect by endogenous and exogenous hormone effects.

Amongst endogenous hormones, androgens have a protective effect. Men with RA show lower levels of testosterone whereas women display lower levels of testosterone and dehydro epiandrosterone sulphate (DHEAS) (Brennan and Silman, 1995). Oestrogen level in serum of patients with RA is normal, and their role in development of RA is controversial (Masi, 1995). Earlier studies demonstrated a protective effect of oestrogen in the development of RA. Contrary to this, oestrogen is found to be protective against the development of rheumatoid factor but not for the development of RA (Bhatia SS, 2007). The role of oestrogen in autoimmunity has also been studied (Lang, 2004). Studies have demonstrated that pregnancy can influence the timing of disease onset. During the post partum period there is an increased risk of development of RA especially after first pregnancy. This effect is seen in the first twelve months after delivery (Alan Silman MD, 1992). Pregnancy improves the severity of RA by 75%. However, an Indian study has not found any association between the onset of RA and pregnancy (Tembe AG, 2008).

Breast feeding for more than 12 months led to an inverse relationship with the development of RA (Karlson EW, 2004). Compared to women who have never breast - fed, breast-feeding for thirteen months or more had a fifty per cent reduction in their risk of development of RA. This risk reduction was twenty five per cent when the duration was less than 12 months. The researchers observed that being multiparous and not breast feeding did not offer the same protective effect. (Pikwer et al., 2009). This study also emphasized that use of oral contraceptive pill did not have similar effects as breast-feeding.

For exogenous hormones, oral contraceptive pills give a protective effect probably due to progesterone (Wingrave, S. J. (1978). The Rochester study demonstrated a fall in the incidence of RA in women taking contraceptive pills (Linos et al., 1980). Recently it was observed that oral contraceptives are protective for the development of rheumatoid factor but not rheumatoid arthritis (Bhatia SS, 2007). A study by Wallit et al in 2008 did not find that HRT use influenced the development or progression of RA (Walitt et al., 2008). However, a study performed in 2009 found that HRT use reduced the risk of developing RA only in those carrying the shared epitope (Carine Salliot, 2010).

1.5.3 Environmental Factors

Studies on population and those involving twins suggest that non- inherited factors such as environmental factors are important in the development of RA. The environmental factors that may influence the development of RA include: infectious agents, smoking, diet and other factors. The role played by these factors is described below.

1.5.3.1 Infection

It was proposed that infection could act as a trigger in the development of RA for genetically susceptible individuals. The infection may be viral or bacterial. Polyarthritis may be caused by viruses like Epstein Barr virus, Parvovirus B 19 and Retrovirus (Blaschke et al., 2000). Immune hyperactivity to viral antigens and their potential in initiating RA has been investigated and their exact role in the development of RA remains to be defined. Bacteria involved in aetiology of RA are Mycobacterium

tuberculosis, E coli and Proteus. Immunizations may also trigger RA in a small number of patients.

1.5.3.2 Smoking

Smoking is the most important and established environmental risk factor in the development of RA. Smoking is a risk factor for the development of RA (Criswell et al., 2002, Hutchinson D, 2001). Cigarette smoking adversely influences the severity of RA in a dose dependent manner (Saag et al., 1997) and it was observed that individuals with a family history of RA had a smoking history similar to controls and lesser than those with a negative family history of smoking (Hutchinson D, 2001).There was an increased association between pack years of smoking and RA. Current smokers have an increased risk of RA which continued till ten years after cessation of smoking. Increased duration of smoking and the number of cigarettes smoked increased the risk of developing RA (Criswell et al., 2002) but association of passive smoking with RA was not observed. Case- control studies have shown an increased risk of developing RA in male smokers compared to females (Krishnan, 2003).

An association exists between smoking and RF positive RA in both genders. Smoking is also associated with increased production of anti CCP antibodies and the risk increases with the number of pack years. The risk of anti CCP positive RA is more in smokers with a single copy for SE and even higher in the presence of double copy. (Klareskog et al., 2006). Smoking was found to be associated with an increased severity of RA in a dose dependent manner (Saag et al., 1997). PTPN 22, HLADRB1 shared epitope and

smoking have a high independent association with the presence of anti CCP antibody and RF is independently associated with smoking and HLADRB1. Smoking is associated with increased risk of RF and anti CCP positivity and is also related with heavy smoking (Morgan et al., 2009). Samples of bronchoalveolar lavage in smokers have shown citrullinated peptides in individuals susceptible to RA (Linn-Rasker et al., 2006). This is mostly seen in patients with HLA- DR shared epitope (Klareskog et al., 2006). There is a gene environment interaction between SE and smoking, anti CCP antibodies and RF (Lundstrom et al., 2009, Oliveira et al., 2008). It has also been observed that heavy smoking is strongly associated with RA in patients without a family history of this ailment (Hutchinson D, 2001). Cigarette smoking is associated with severe arthritis and it was demonstrated in a cross-sectional study that smoking is associated with erosive disease (Wolfe, 2000b). Extra articular manifestations are increased in Caucasians and Koreans who smoke (Nyhall-Wahlin et al., 2006, Kim et al., 2008), and presence of sub cutaneous nodules has been observed in RF positive smokers. A study in African Americans demonstrated a two-fold increase of subcutaneous nodules in smokers (Mikuls et al., 2008).

Smoking is also associated with interstitial lung disease and premature death due to CVD. However, a study by Wallberg Jonson et al failed to identify smoking as a risk factor for CVD mortality in a RF positive RA cohort (Wållberg-Jonsson, 1997). In the Norfolk Arthritis Registry (NOAR) it was demonstrated that inflammatory poly arthritis patients that smoked at inception had an increased risk of death which was higher when anti CCP antibody was positive and two SE alleles were present (Farragher et al., 2008).

For individuals without RA, smoking may be associated with production of rheumatoid factor. And RF has been identified as a risk factor for mortality in the absence of RA in a Finnish population study (Heliovaara et al., 1995).

Rates of smoking are low in Indian men when compared with other Asian countries like Japan, China etc and smoking in South Asian Indian women is negligible.

1.5.3.3 Other factors

The exact role of diet in the development of RA is not clear yet (Pattison et al., 2004). Increased intake of fruits, vegetables and nuts or reduced intake of meats and processed foods may help in better symptom management. The association between RA and dietary factors like fish consumption which has a protective effect has been (Pedersen et al., 2005) studied and it was found that it modifies the risk of RA. Use of caffeine is reported to moderately increase the risk of RF positive and not RF negative RA (M Heliovaara, 2000). Tea consumption has an inverse relation to onset of RA due to its anti-inflammatory and anti- oxidant properties (Mikuls, 2002). There are studies which did not find an association between RA and the consumption of these beverages (Karlson EW, 2003). Increased intake of red meat was associated with increased risk of development of inflammatory arthritis (Dorothy J. Pattison, 2004) but no relation between the amount of protein, red meat, poultry, fish and the modification of RA risk was observed in other studies (Pedersen et al., 2005, Benito-Garcia et al., 2007). Alcohol has a negative association with RA (Hazes et al., 1990). Women above 55

years did not demonstrate an association between alcohol and the risk of RA (Cerhan et al., 2002).

The development of RA has an inverse association with socio economic status, level of education and occupational class (Bengtsson C, 2005). The difference in the risk of developing RA may be attributed to changes in life style, socio economic status and access to health care (ERAS study group (2000). There is an inverse association between RA and the level of education. A population based case control study demonstrated an increased risk of RA in persons doing manual labour and having a lower level of education. This association was more with RF positive RA (Bengtsson C, 2005). Adverse socioeconomic status is associated with worse disease outcome. Low level of education reduces the presentation of self reported arthritis and is associated with poor clinical state and increased mortality.

Previous studies stated that obesity is linked with the development of rheumatoid arthritis (Voight, 1994). However, in the light of recent results obesity has no effect on the risk of development of RA. BMI was inversely associated with radiological damage during three years of follow up (van der Helm-van Mil et al., 2008). Another study found no association between obesity and risk of RA (Cerhan et al., 2002). In established RA, obesity was found to be associated with active disease and not erosions(Antonios Stavropoulos-Kalinoglou, 2007). A study of Indians with RA reported an inverse association between high BMI and erosive joint damage (Velpula U, 2008).

Variation in latitude may influence the onset of RA. In individuals from northern latitudes the disease onset is earlier (Vieira VM, 2010).

High birth weight has been shown to be associated with increased risk of RA in one study conducted in Sweden (Lisa A. Mandl, 2009) .

1.6 Co morbidity in rheumatoid arthritis

Patients with RA have an increased risk of death compared with age and gender matched normal controls from the same community. Reports of RA related mortality have been published as early as 1950 (Spector and Scott, 1988). In chronic RA the median life expectancy is less than controls. The life expectancy in men with RA is reduced by 7 years and 3 years in women (Spector and Scott, 1988).The reasons for this increased mortality may reflect the increased co morbidity associated with RA.

A co morbid condition is another medical condition that is present in association with RA. Studies have demonstrated that 27- 54 % of RA patients have a co-existent disease. Co morbidity independently predicts mortality (Vandenbroucke et al., 1984). The number of co morbidities is an independent risk factor for premature death (Gabriel et al., 1999b). The major co morbidities recognized in RA are cardiovascular disease, infection, malignancy, gastro intestinal disease and osteoporosis. The system specific co morbidities in RA are elaborated in Table 1.5. These co morbidities are major determinants of disease-associated outcomes.

Co morbidities are also common in Indian patients with RA. One co morbidity has been reported in 44% of established RA patients and 15% had two co morbidities. The most common co morbidities observed in this study were hypertension and diabetes and 2.5% of patients had diagnosed CVD (Tembe AG, 2008).

Table 1.5 Mortality in rheumatoid arthritis (Pincus and Callahan, 1986)

Cause of death	RA (%)
Cardiovascular	42
Infection	9.5
Cancer	14
Renal	8
Respiratory	7
Gastrointestinal	4.2

1.7 Cardiovascular disease

Cardiovascular disease (CVD) is a leading cause of mortality in patients with RA and accounts for nearly half of all deaths (Symmons et al., 1998). Symmons et al studied the United Kingdom National Health Service Central Register and reported a standardized mortality ratio of 2.2 (95% confidence interval 1.8-2.6) for CVD in RA patients (Symmons et al., 1998). CVD accounted for 34% of excess deaths in this population.

Cross-sectional studies of mortality in RA include individuals irrespective of the disease duration and during follow up individuals in remission may be lost. Patients with active disease continue to attend rheumatology follow up and therefore these studies will tend

to include patients with more severe or active disease. Inception cohorts tend to include individuals with early disease and follow them as the disease evolves over time. This study design provides a better estimate for comparing mortality with the general population, whereas cross-sectional studies of standardized mortality rate (SMR) will observe mortality at a given point of time.

Studies involving inception cohorts showed mixed results, some studies did not show increase in incidence of CV mortality (Kroot et al., 2000) while others demonstrated an increased CV mortality (Goodson et al., 2005a). A recent meta- analysis of cohort studies investigating the effect of RA on CV mortality has documented that though RA disease activity has reduced in past five decades the CV mortality in RA patients continues to be unchanged and is 60 % more when compared with the general population. It was pointed out that the effect of RA disease severity, treatment and traditional CV risk factors should be considered in accounting for the increase in CVD mortality (Meune et al., 2009). The risk of CVD is falling in the general population. It was reported in a meta-analysis that there is a 50% increase in CV mortality in RA patients when compared to general population and no gender difference in mortality was observed (Avina-Zubieta et al., 2008). The studies included in this meta-analysis were from Europe and North America and majority of the studies were clinic based.

The World health organization (WHO) has reported that CVD mortality in Indians in 1990 was 1.2 million and by 2010 it is estimated that 100 million Indians will have CVD, which amounts to 25% of CVD all over the world. The CVD mortality is predicted to reach highest in the world by 2020 (Murray and Lopez, 1997, Reddy and

Yusuf, 1998). Till date no data on CV mortality in RA patients from India has been found in the literature.

The pathogenesis of CVD in RA is multi factorial and can occur in the form of coronary heart disease, cerebrovascular disease or peripheral vascular disease. There is a strong association between chronic inflammation and CVD. C reactive protein (CRP) is a non specific inflammatory marker which is an independent risk factor for CVD (Goodson et al., 2005a). A study involving apparently normal physicians followed up for eight years concluded that level of chronic inflammation predicts the risk of CVD in normal individuals (Ridker et al., 1997). It has been demonstrated that mortality is increased in patients with RF positive disease (Wolfe et al., 1994, Heliovaara et al., 1995, Wallberg-Jonsson et al., 1997, Goodson et al., 2002, Gonzalez et al., 2008a).

The traditional cardiovascular risk factors can be classified as modifiable and non-modifiable (Table 1.6). The modifiable risk factors are directly proportional to the risk of CVD which can be reduced with proper identification and intervention. The traditional risk factors are linked to CVD in general population and have also been implicated in the setting of RA. These interact with each other to give a composite CVD risk score (Dessein and Joffe, 2006b). The QUEST RA study confirms the association of traditional risk factors in the development of CVD (Naranjo et al., 2008).

Table 1.6 Traditional risk factors for CVD

Male gender	Non Modifiable
Increasing age	
Family history of CHD (coronary heart disease)	
Hypertension (HTN)	
Diabetes Mellitus (DM)	
Smoking	Modifiable
Physical inactivity	
Obesity	
Increased T Cholesterol	
LDL Cholesterol	
Triglycerides	
Decreased HDL Cholesterol	

In addition to traditional CVD risk factors novel risk factors like homocystine, thrombotic markers such as elevated fibrinogen, impaired fibrinolysis, platelet reactivity and markers of inflammation like elevated CRP and elevated Lipoprotein `a` are also important in the risk of CVD. Plasma homocystine levels are independently associated with CVD in Caucasians and Indians (Chambers et al., 2000). But homocystine levels are not associated with CVD in South Indians, as studies have not demonstrated a difference in patients with and without CAD. High plasma fibrinogen levels are associated with CAD this is also reported in south Indians (Deepa et al., 2002). Lipoprotein 'a' levels are genetically determined and high levels are associated with CVD. Indians exhibit high levels of lipoprotein 'a' (Enas et al., 1997).

It is difficult to know the exact cause of death in RA as the increased mortality could be due to the effect of the disease or the medicines used to treat the disease. Medications

used to treat RA may have an effect on the CVD risk. Methotrexate is found to decrease CVD mortality (Choi et al., 2002). In a recent study evaluating published literature regarding methotrexate (Mtx) and CVD it was observed that Mtx use in RA was associated with a trend for reduced CVD morbidity and mortality. This benefit was observed especially when Mtx was started in early disease (Westlake SL 2009). NSAIDs and glucocorticoids tend to increase the CV risk but their effect is controversial (Souverein et al., 2004, Goodson et al., 2009, Gislason et al., 2009). Goodson et al explored the association of CVD mortality and NSAID use in an inception cohort of inflammatory polyarthritis in the NOAR. The patients were followed up for an average of 10.7 years. Mean NSAID use was 4 years. Reduced CVD mortality was observed in baseline NASAIDs users and in patients with a history of ever use of NSAID. When gender was taken into consideration death rate in males was twofold higher compared to females. Overall the NSAID users had more than two-fold decreased risk of CVD mortality. The authors concluded that the reduced CVD mortality in NSAID users might be attributed to the doctors avoiding NSAIDS in high-risk patients, the effect of unmeasured confounders and the possibility of anti platelet effect of NSAIDS. In contrast Gislason et al studied the effect of NSAIDs in patients with heart failure and observed their risk of death and hospitalization due to myocardial infarction and heart failure. In this high-risk population the authors demonstrated a dose dependant increase in death and gave a word of caution for the use of NSAID in patients with heart failure. The effect of various drugs used in the management of RA is described in chapter 2.

1.8 CVD in Indians

CVD in Indians is two times higher than Caucasians and four times higher than Chinese (Miller et al., 1989, Lee et al., 2001) and it occurs one decade earlier, is more severe, aggressive and has a malignant course (Enas et al., 1992). The prevalence of CAD is high among Indians living in India and continues even if they live abroad. The KAISER study demonstrated that Indian patients had a four times increased rate of hospitalization for coronary interventions like angioplasty and bypass surgery when compared with American patients (Klatsky et al., 1994). This increased prevalence agrees with the results of CADI study (Enas et al., 1992).

The prevalence of CVD is found to be similar in vegetarians and non-vegetarians. Residents of urban areas have a two-fold increase in CVD when compared to rural areas and marginally higher in south Indians when compared to north Indians (Mohan et al., 2001, Chadha et al., 1990). Earlier it was assumed that Indians had a high prevalence of CVD despite having lower prevalence of CV risk factors -"Indian paradox". This theory is not applicable now as it has been established that India is emerging as the diabetic capital of the world (Zimmet P 1992, Shashank R Joshi 2004) and may also become the hypertension capital of the world (Ramachandran A 2001, Mohan V 2007).

Metabolic syndrome is emerging as a major health problem in Indians mainly from urban areas. The prevalence of overweight, obesity and abdominal obesity in 30 – 60 % of adult urban Indians was demonstrated (Misra A 2004). This has a direct correlation

with occurrence of obesity related co morbid conditions like hypertension, diabetes, dyslipidaemia and CVD (Gupta R 2002).

The CVD rates in India have doubled in the past three decades and it is predicted that an epidemic of CVD is fast approaching (Reddy and Yusuf, 1998, Enas, 2000). Traditional CVD risk factors remain the main focus of attention in the prevention and treatment of CVD. In the general population these risk factors are strong predictors of CVD outcome including mortality and morbidity. All the CV risk prediction scores utilize traditional CVD risk factors for the estimation of 10-year risk of CHD.
Cardiovascular co morbidity in RA forms the basis of this research in patients from Hyderabad in South India. A historical review of the literature is given in chapter two.

In summary, although the aetiology of RA is not completely known, it is thought to be caused by the interaction of several risk factors. The presence of coexistent disease plays an important role in the outcome of RA. With the above background, considering the lower prevalence of RA in India and consequently fewer studies reported, my work was undertaken. The important aspect is that CV risk in RA has been extensively studied in large populations but these studies were done for Caucasians. Moreover with the current trends amongst the Indian population, their genetic orientation and increased susceptibility towards cardiac and ischemic complications, it was felt worthwhile to examine and correlate the prevalence of CV risk factors in Indian patients with RA. The effect of disease modification on the CV risk factors is also studied.

Chapter 2 - Background Literature Review

2.1 Introduction

This chapter provides a review of literature pertaining to mortality in rheumatoid arthritis and its associated morbidity. Traditional cardiovascular risk factors in rheumatoid arthritis are described in detail. The 10 year risk prediction of a cardiovascular event is discussed. RA disease parameters contributing to increase in CV risk and the cardiovascular effects of medicines used in the treatment of RA are elaborated.

2.2 Mortality in Rheumatoid arthritis

2.2.1 Cardiovascular mortality

Rheumatoid arthritis (RA) is associated with disability, deformity and reduced life expectancy. Increased mortality associated with RA has been recognized for fifty years (Cobb et al., 1953). Mortality in patients with RA is increased when compared to the general population (Sokka et al., 2008), (Sihvonen et al., 2004a), (Watson and Fisher, 2003), (Gabriel et al., 2003). The lifespan of RA patients is decreased approximately by 3-18 years (Van Doornum et al., 2002). One of the major causes of death in RA is due to cardiovascular disease (CVD) (Reilly et al., 1990, Wolfe et al., 1994) which is responsible for about fifty percent of premature deaths (Van Doornum et al., 2002, Naz and Symmons, 2007). This increased CV mortality is multifactorial and is attributed to traditional CV risk factors, novel risk factors, systemic inflammation due to RA and

medicines used in treatment of RA (Avina-Zubieta, 2008). Despite advances in treatment, mortality in RA has not changed over the past 50 years (Meune et al., 2009).

A meta-analysis of 24 observational studies from the UK and USA reported that RA patients had a 50% increased risk of CV deaths when compared to general population. The increased mortality was due to excess deaths coded as Ischemic Heart disease (IHD) and cerebrovascular accidents (CVA). Higher mortality was seen in patients fulfilling American college of rheumatology (ACR) criteria. No gender difference was observed (Avina-Zubieta et al., 2008).

Kumar et al compared cause of death in 257 RA patients, 374 same gender siblings and matched 485 osteoarthritis (OA) patients, by reviewing death certificates found that there were 54% deaths in RA versus 28% in siblings and 32% in OA. More deaths in RA and OA group were due to IHD. Interestingly, RA patients had a 40% reduced cancer related death than expected compared to their siblings (Kumar et al., 2007).

Rheumatoid factor (RF) has an impact on mortality (Heliovaara et al., 1995, Wallberg-Jonsson et al., 1997, Goodson et al., 2002). A study of 1010 RA patients by Goodson et al reported that mortality was higher in RF positive women when compared to RF negative women and both RF positive and RF negative men. The increased mortality trend in RF positive patients was further confirmed by another study reporting increased deaths in RF positive patients compared to RF negative patients and the general population. The mortality trend in RF negative patients may be similar to the general

population (Gonzalez et al., 2008a). Anti cyclic citrullinated peptide (CCP) was found to be strongly associated with mortality (Farragher et al., 2008, Mackey, 2010).

In an autopsy study of 369 RA and 370 non RA patients the leading cause of death in RA patients was CVD and infection. Over more recent years, a decline in CV related deaths was observed in the non RA group and not in the RA group. The autopsy based deaths were similar in the RA group irrespective of RA treatments. The authors concluded that coronary deaths were less accurately diagnosed in RA which may be an indicator of unrecognized coronary artery disease in RA (Koivuniemi et al., 2008). RA patients have different presentation of IHD when compared to general population (Maradit-Kremers et al., 2005). They may have unrecognized silent IHD and no typical chest pain before sudden death (Douglas et al., 2006).

An article discussing the importance of study design, in interpreting studies of CV mortality, mentioned that inception cohort studies are able to capture a CV event after the onset of disease compared to prevalence cohorts which include survivors of an event and do not provide information on patients who may have died from CV prior to being included in the prevalence cohort. Therefore, when assessing rates of CV events, use of prevalent RA cohorts may lead to an underestimation of the true mortality rate. There is also a relation between onset of RA and the time of CV death (Ward, 2008). An inception cohort study reported increased mortality in patients with RA but the rate of hospital admission in RA patients for CVD was not increased. This may be either due to

CVD being under recognized in RA or due to higher fatality rates in RA (Goodson et al., 2005a).

2.2.2 Other causes of mortality in rheumatoid arthritis

In addition to CV mortality, RA patients are at an increased risk of death from various other causes. These include infections, respiratory causes, urogenital, gastrointestinal and cancers. The rate of death from these causes is higher when compared to the general population (Sihvonen et al., 2004a).

After CVD, infection is the second most common cause of mortality in RA. The risk of infection increases with the duration of RA (Symmons et al., 1998). Respiratory infections in the form of pneumonia and chronic pulmonary obstructive disease and pulmonary fibrosis have been observed (Hakoda et al., 2005, Young A, 2006).

Not many studies have found increased risk of cancers in patients with RA compared to general population. Indeed, Kumar et al reported a lower rate of cancer related deaths in RA patients compared to age and gender adjusted population rates (Kumar et al., 2007). However, when site specific malignancy rates have been explored, higher rates of non Hodgkin's lymphoma and lung cancers have been observed (Naz and Symmons, 2007).

In a study looking at renal disease in RA including 604 RA patients and 457 age and gender matched controls it was observed that nephropathy is associated with increased mortality in RA (Sihvonen et al., 2004b).

2.3 Studies in non Caucasian populations

Most of the mortality studies are conducted in Caucasian RA population. There are very few studies reporting mortality in RA from Asian countries. One study following up RA patients for forty years in Japan observed that RA patients had increased mortality when compared to non RA population. Mortality due to CVD was the highest (34.9%), followed by respiratory causes (15.7%), cancer (14.5%), gastrointestinal (6%) and renal (2.4%) (Hakoda et al., 2005).

We are not aware of any published study addressing mortality in South Asian Indian patients with RA. Many studies have been published that study the general population and have observed CVD as a major cause of death in South Asian Indians (Mohan et al., 2001, Enas et al., 1992). The mortality rate in South Asian Indian RA patients is still unknown. It is not clear whether having RA further increases CVD mortality rates above the high level observed in the Indian population.

2.4 Co morbidity in Rheumatoid Arthritis

Co morbidity is defined as a medical condition that coexists with the disease of interest. An RA patient is said to have an average 1.6 co morbidities and the number increases with the patient's age (Gabriel SE, 2008). In the literature co morbidity in RA usually refers to presence of CVD, infection, malignancy, osteoporosis etc (Gabriel, 2008, Michaud and Wolfe, 2007).

2.5 Traditional CV risk factors

Mortality from CVD, among the general population is predicted by traditional CV risk factors. Many studies have observed increased prevalence of these risk factors in RA (Brady et al., 2009, Erb et al., 2004, Serelis et al., 2011, Naranjo et al., 2008, Innala et al., 2011) and others have found the occurrence similar to the general population (del Rincon et al., 2001, Solomon et al., 2004). A recent meta-analysis has confirmed the role of traditional CV risk factors in increased CVD observed in RA (Boyer et al., 2011). The modifiable and non modifiable traditional CV risk factors are given in Table 1.6.

2.6 Modifiable traditional CV risk factors

2.6.1 Hypertension

Hypertension (HTN) is one of the modifiable traditional risk factor and a major contributor in the development of CVD. A systolic reading above 140 mm of Hg and a diastolic reading above 90 mm of Hg is considered as hypertension in accordance with guidelines from the British Hypertension society and National cholesterol education programme - Adult treatment panel (NCEP ATP)(NCEP, 2001, Bryan Williams 2004). However, it has been documented that as little as a 10 mm of Hg rise in diastolic BP doubles the risk of development of heart attack, stroke, renal failure and heart failure. In individuals aged less than 50 years of age, diastolic BP is the most important predictor of an adverse outcome (Perry et al., 2000). According to the Framingham Heart study the CV risk was weakly associated with diastolic BP but a

much stronger CV event association was observed with systolic BP above 120 mm of Hg. (Kannel, 2000). It is also shown that obesity and advancing age are strongly associated with HTN.

McEntegart et al (McEntegart *et al.* 2001) found that a cohort of established RA patients had higher diastolic blood pressure than age and gender matched controls. Most of the patients in this study were using NSAIDs to treat symptoms of RA. However, previous research has suggested that NSAID usage is more likely to lead to an increase in systolic BP rather than diastolic BP (Frishman 2002). It is possible that there is some other mechanism associated with RA that may have caused this rise in diastolic BP. Hypertension was reported in 33% of participants in the QUEST-RA (Questionnaires in standard monitoring of patients with RA) study which was conducted in 4,363 RA patients from 15 countries across Europe and America (Naranjo et al., 2008) . Many studies reflect that hypertension may be present in patients with RA as a co morbid condition or evolve in the course of the disease (Goodson, 2002), (Kroot et al., 2000, Serelis et al., 2011, Panoulas et al., 2008) for which the use of NSAIDS and glucocorticosteroids may be responsible. Recently it was reported that hypertension in RA was similar to the general population (Boyer et al., 2011). There is a possibility of hypertension being unrecognized or under treated in RA.

A meta-analysis addressing the global burden of hypertension stated that nearly 1 billion of the general adult world population had hypertension in year 2000 and this was anticipated to increase to 1.56 billion by the year 2020. Hypertension was found to be

more common in developed countries (37.3%) when compared to developing countries (22.9%) but due to increased population of developing countries, the individual affected is larger (Kearney et al., 2005). Hypertension in urban north Indians was 25% in males and 22.3% in females and the prevalence in west Indian urban population was found to be 30% in males and 33% in females (Kearney et al., 2005). The prevalence in Indians in rural areas was found to be less than that seen in urban regions (Mardikar and Mukherjee, 2007). Kerala, South India has reported a prevalence of hypertension of 37% in 30-64 year old individuals (Zachariah et al., 2003). A study of hypertension in the UK observed that the blood pressure in South Asians and European adults was similar (Agyemang and Bhopal, 2002). However, another study has reported that South Asians have a higher prevalence of high diastolic blood pressure (Ajjan et al., 2007).

2.6.2 Diabetes

Diabetes is another modifiable risk factor for CVD. Diabetes is also an important constituent of the metabolic syndrome. Not many studies have explored the prevalence of diabetes in RA. Most of the published literature reports diabetes as part of the CV risk assessments. The QUEST RA study reported an 8% prevalence of diabetes in Caucasian RA patients (Naranjo et al., 2008). However, prevalence of diabetes was reported to be increased in RA when compared to general population (Boyer et al., 2011). Prevalence of type II diabetes may be increased in RA due to reduced activity in active RA and the medications used in treatment of RA. Chronic use of glucocorticoids may interfere with glucose metabolism and insulin sensitivity as well as being associated with adverse body fat accumulation (Dessein et al., 2004). When compared

to low grade inflammation, high grade inflammation in RA was found to increase insulin resistance and reduce beta cell function resulting in impaired fasting blood glucose and diabetes (Dessein PH, 2006).

The thrifty gene hypothesis may be applied to individuals from developing countries. The thrifty gene hypothesis suggests that genetic variations are favoured in harsh environments where famine situations occur. It is hypothesised that these genetic variants enable an individual to efficiently collect and process food to deposit fat during periods of abundance. Therefore this induces these individuals to develop obesity when they reside in food rich environments. In addition as intra uterine growth retardation results in a tendency to catch up growth in infancy and causes an increased tendency to develop obesity and type 2 diabetes in adulthood. South Asian Indians are more prone to develop diabetes which may be due to increased susceptibility to insulin resistance (McKeigue PM, 1991).

Diabetes is seen in South Asian Indians about a decade earlier when compared to other Asians and Caucasians (Mather HM, 1998). India has the highest number of diabetics in the world (Gupta R, 2007). In India an estimated 32 million people suffer from diabetes and the number is projected to increase to 69.8 million by the year 2025. The diabetes epidemiology and study group in India (DESI) reported prevalence of Diabetes in urban Indians is 11.6% and a study has reported that one in four urban Indians above 20 years have either impaired glucose tolerance or diabetes (Ramachandran A, 2001). The highest prevalence of diabetes was observed in Hyderabad, India (16.6%) in the same

study. According to a survey published in a leading national daily – The Hindu business line (21 Oct 2005) Hyderabad, a city of over eight million inhabitants is emerging as the diabetic capital in India. There are no case control studies addressing the prevalence of diabetes in South Asian Indians with RA.

2.6.3 Smoking

Smoking is an important constituent of CV risk assessment and is a modifiable CV risk factor. As discussed in the introduction chapter, smoking has been shown to be related in the development of RA. When compared to controls in a UK study, smoking was found to be increased in RA (Hutchinson D, 2001) in a dose dependent manner. Increased mortality is associated with smoking in RA and the general population (Goodson et al., 2008). In a study of 603 RA patients and 603 non RA controls followed for 15 years it was found that male gender, smoking and personal cardiac history all had a weak association with CVD (Gonzalez et al., 2008b). However, another study confirmed an increased prevalence of smoking in RA (Boyer et al., 2011). The QUEST-RA study described a prevalence of ever smoking in RA to be 43% (Naranjo et al., 2008).

Studies of smoking have reported lower smoking rates among South Asian Indians compared to European populations (Yuen, 1986, Agyemang C, 2010). Similar reports are there from South Asian Indians from United States of America (Cristine D. Delnevo, 2011). Data regarding smoking in Indians is limited. Smoking is almost

nonexistent in South Asian Indian women but they have CVD comparable to men (Enas EA, 2001).

2.6.4 Lipids

Dyslipidaemia is an important risk factor for CVD in the general population NCEP ATPIII (III, 2002). Dyslipidaemia is observed in RA patients (Situnayake RD (Kitas, 1997). When compared to the general population, hyperlipidaemia is less frequently observed in RA (Gonzalez et al., 2008b). However, dyslipidaemia was observed in 14% of RA patients enrolled in the QUEST-RA study (Naranjo et al., 2008). Lower total cholesterol and LDL cholesterol in RA were found to be associated with CV risk (Elena Myasoedova and Patrick D Fitz-Gibbon, 2011). The abnormal lipid profile especially low HDL cholesterol was associated with RA and reduction in RA disease activity was found to improve dyslipidaemia (Urowitz, 2009). Active RA is associated with dyslipidaemia. The characteristic change being low total cholesterol , low density lipoprotein (LDL) cholesterol and disproportionate lowering of high density lipoprotein (HDL) cholesterol which results in an unfavourable atherogenic index (ratio of total cholesterol to HDL cholesterol). Lipids have an inverse relationship with disease activity (Situnayake RD (Kitas, 1997). In active disease there is increase in the circulating pro inflammatory cytokines which promote the development of rheumatoid cachexia wherein there is increased fat mass and reduced lean muscle mass (Kitas and Gabriel, 2011). There by active RA patients when compared to normal controls have increased fat mass at a lower BMI (Stavropoulos-Kalinoglou A, 2007).

When compared to Caucasians, Indians tend to have lower HDL cholesterol and higher triglycerides (McKeigue PM, 1991). South Asian Indians are known to have a high prevalence of dyslipidaemia in the usual lipid pattern with elevated total cholesterol, high triglycerides and low HDL cholesterol (Anand et al., 2000).

2.7 Non modifiable CV risk factors

Increasing age, male gender and family history of CVD are non modifiable traditional CV risk factors. The risk of CHD increases with increasing age (NCEP, 2001). Male gender is an independent risk factor for CVD (Pekka Jousilahti, 1999). Most of the studies in RA have addressed prevalence of traditional CV risk factors in women (Solomon et al., 2004, Roman et al., 2006, Dursunoglu D, 2005) ; very few studies mention the occurrence of CV risk factors in males with RA (Mikuls et al., 2011) and this reflects reduced prevalence of RA in males. Whilst there is some comparative data looking at CV risk factors and CV risk scores in males and females with and without RA, some of these studies have reported conflicting findings. Family history of premature CHD is defined as CHD in first degree relative male less than 55 years and female less than 65 years (NCEP, 2001). Family history of CVD was more frequently reported in RA patients when compared to controls from the general population (Feldman, 1991). South Asians Indians have a strong family history of premature CHD (Enas et al., 1992). The family history of CHD in the context of RA has not been studied in this population.

2.8 Metabolic Syndrome

Metabolic syndrome (MS) is a cluster of cardiovascular risk factors. The clustering of metabolic abnormalities occur in the same individual and increase CV risk more than the sum of the individual components (Reilly and Rader, 2003). The MS is also called insulin resistance syndrome, syndrome X and Reavens syndrome. This syndrome was first described in 1988 by Reaven who found that multiple risk factors like dyslipidaemia, hypertension, and hyperglycaemia cluster together in CVD and called it syndrome X (Reaven, 1988). However, abdominal obesity was not included. There are different definitions of metabolic syndrome. The most commonly used definitions are provided by 1) world health organization (WHO), 2) the national cholesterol education program adult treatment panel III (NCEP ATPIII) and 3) the international diabetes federation (IDF). It was demonstrated that the odds ratio using different definitions of metabolic syndrome NCEP ATPIII (OR 2.00), WHO (OR 1.73) and IDF (OR 1.69) was almost similar in predicting incident CHD which was independent of ethnic origin, age, gender, family history of CVD, smoking, T2DM, CHD, and non HDL C (Lorenzo et al., 2007). The NCEP ATP III is simpler and the most widely used in clinical practice. The criteria are similar. The WHO requires evidence of insulin resistance. But according to NCEP ATPIII measuring insulin resistance should not be included as this is so strongly associated with type 2 DM.

Three out of the following five criteria are to be met for an individual to be classified as metabolic syndrome NCEP ATP(III, 2002).

Table 2.2 Criteria for metabolic syndrome

Risk Factor	Cut off point
Waist circumference	>102cm(>40 inches) in males > 88cm (>35 inches) in females
Triglycerides	≥150mg / dl
Low HDL	Male < 40mg / dl, Female <50mg / dl
Blood pressure	>130/85 mm of Hg or an antihypertensive
Fasting blood sugar	>110 mg/dl or diabetes

The presence of metabolic syndrome increases an individual's risk of type 2 Diabetes, and also the risk for CVD. Individuals with MS are at an increased risk for CHD (Lakka et al., 2002). The increased prevalence of CVD in RA has led to an association with metabolic syndrome. Inflammation is an important feature in obesity, type 2 DM and in patients with chronic inflammatory diseases like RA. High prevalence of MS (44%) was observed in middle aged RA case control study and there was a correlation observed between increasing level of RA disease activity and MS (Karvounaris et al., 2007). In a recent case control study in persons without a history of CVD, RA was more likely to be associated with MS (Crowson et al., 2011). Dessien et al examined 79 RA patients vs 39 patients with osteoarthritis (OA) and found an association between CRP, insulin sensitivity, HDL cholesterol, triglycerides and hypertension with RA and not OA (Dessein et al., 2002). In a later study the authors reported the association of high grade inflammation with high insulin sensitivity when compared to low grade inflammation (Dessein and Joffe, 2006a).

Studies have correlated insulin resistance and atherosclerosis in RA patients. Significant association was found between carotid intima media thickness and insulin resistance in 45 RA patients compared to 45 controls (La Montagna et al., 2007). Another study found that hypertension, insulin resistance and triglycerides were associated with carotid intima media thickness and presence of plaque (Dessein et al., 2006). High prevalence of metabolic syndrome was observed in RA: patients with long standing disease had higher occurrence of MS (42%) when compared to early RA and controls (30% and 22%) (Chung et al., 2008). Other studies did not have an association of MS with disease duration (Karvounaris et al., 2007, Crowson et al., 2011).

Increased waist circumference is an important constituent of MS. RA patients demonstrated 4 times increased likelihood of having high waist circumference even after adjusting for BMI (Crowson et al., 2011). Another study measuring body composition found that RA patients, compared to controls had increased fat mass and decreased muscle mass (Giles et al., 2008). Rheumatoid cachexia is an abnormal body composition with increase fat mass and reduced muscle mass. These changes can occur with a normal or increased BMI. Active disease is frequently (30%) associated with rheumatoid cachexia (Engvall et al., 2008, Giles et al., 2008). Loss of muscle mass is attributed to increased circulation of pro inflammatory cytokines especially tumour necrosis factor alpha (TNF) resulting in increased disease activity and reduced physical activity which further reduce the muscle mass and increase the fat mass (Summers et al., 2010). In an article reviewing metabolic syndrome in rheumatic disease the authors found high prevalence of traditional CV risk factors and MS and have advised

assessment of MS and 10 year of CHD risk in patients with rheumatic diseases (Sidiropoulos et al., 2008).

Most of the published literature addressing MS in RA is based on studies performed in Caucasians. Caucasians from a general non RA population have a lower occurrence of MS when compared to South Asians (Misra and Khurana, 2011). The prevalence of abdominal obesity was high in young South Asians, even at a BMI <25 kg/m2 (Vikram et al., 2003). Lower insulin sensitivity index and lower glucose disposal was seen in Asian Indians when compared with Caucasians (Misra and Khurana, 2011). South Asians with metabolic syndrome had higher diastolic blood pressure, triglycerides, HDL-Chol and fasting insulin when compared to Caucasians (Ajjan et al., 2007). South Asian Indian migrants have high prevalence of MS compared to native populations and other ethnic groups (Misra and Misra, 2003, Tan et al., 2004).

The International day for evaluation of abdominal obesity study evaluated abdominal obesity in 63 countries and found that South Asians had the highest prevalence of abdominal obesity when compared to North Europeans and other Asians (Balkau et al., 2007). Among South Asian Indians there is a difference in the MS in residents from urban and rural areas and from various parts of India. Urban residents have an increased prevalence of MS. Data suggests that one third of urban residents from large cities have MS (Ramachandran et al., 2003). South Indians are found to have high abdominal obesity, hypertriglyceridaemia, low HDL-Chol, increased frequency of hypertension and high fasting blood glucose (Ramachandran et al., 2003) whereas non obese north

Indians had high prevalence of T2DM, hypertension and hypertriglyceridaemia (Vikram et al., 2003). MS differs among genders; women have one and a half to two times increased prevalence of metabolic syndrome compared to men (Wasir JS, 2007). Women from south India have higher MS compared to north Indian women (46.5% vs 36.3%) (Ramachandran et al., 2003, Reddy KS, 2006).

Sub-clinical inflammation is associated with metabolic syndrome (Ridker et al., 2003) and increased risk ofT2DM and CHD (Indulekha et al., 2011). High sensitivity CRP (Hs CRP) was found to be elevated in 46% of post menopausal South Asian Indian women with multiple CV risk factors (Wasir JS, 2007). The increased Hs CRP levels were twice that of Caucasians (Forouhi et al., 2001).

In view of ethnic variations in body composition, new data cut off for waist circumference and BMI have been introduced by NCEP ATPIII, WHO and IDF. However, their predictive value in identifying type 2 DM and CVD compared to earlier cut off has been debated (Misra and Vikram, 2008).

In view of the high background prevalence of MS syndrome in South Asian Indians, it would be interesting to explore whether chronic inflammation associated with RA increases this prevalence further. Surprisingly there are no published studies on metabolic syndrome in South Asian Indian RA patients.

2.9 Body Mass Index and waist hip measurements

The body mass index of an individual is calculated by dividing an individual's weight in kilograms (kg) by height in meter square (kg/m2). The world health organization has classified obesity based on BMI values (WHO, 1995) see Table 2.3

Table 2.3 WHO Classification of Obesity

Classification	BMI (kg/m^2)
Normal	< 25
Overweight	25 - 30
Obese	>30
Class I	30 - 35
Class II	35 - 40
Class III	> 40

South Asian Indians exhibit higher risks of CVD at a lower BMI, hence lower cut offs were suggested for various ethnic groups. However, there is no consensus of opinion in when these should be used and there is debate about interpreting the results (James WPT, 2002, WHO, 2004).

The waist to hip ratio is a ratio of waist and hip circumference and is a measurement of obesity. Based on these measurements, the body type is described. Increased distribution of fat around the waist results in apple shaped body and when the fat distribution is more around the hips results in pear shaped body. The "apple shaped" body type is associated with adverse health risk. Increased abdominal circumference is a part of the metabolic syndrome as discussed already in section 2.8.

2.10 Cardiovascular risk assessments

Traditional CV risk factors form the basis of CV risk estimation by various methods. These methods are used to predict the percentage risk of a CV event in the next ten years. Many countries have adopted different scoring systems. Worldwide, the most commonly used CV risk estimation method is the Framingham CV risk assessment. Other CV risk assessment methods are the Joint British CV risk estimation scores, the systemic coronary risk evaluation model (SCORE), Reynolds risk score and the recent QRISK prediction scores. Apart from the QRISK prediction score all the other CV event prediction algorithms have been developed using data derived from the Framingham Heart Study.

The Framingham heart study started in 1948 with 5,209 adults from the town of Framingham in Massachusetts, USA. This is a predominantly Caucasian population. This study has resulted in long term follow up of individuals. The second generation of participants were enrolled in 1971 and is presently following up the third generation of participants, which started in 2001. Most of the published literature regarding the epidemiology of CHD is derived from this study.
(http://www.framinghamheartstudy.org/about/milestones.html)

From the results of this study it was known that CHD is influenced by lifestyle, environmental factors and inheritance. The individual CV risk factors are used to predict the probability of a CHD event in men and women (Peter W. F. Wilson, 1998).

This CV risk prediction model is widely used in South Asian Indians (S Kanjilal, 2008). The Framingham risk prediction model is based on seven domains given in Table 2.4.

Table 2.4 Seven domains of Framingham risk score

Constituents of the Framingham risk scores	
Age	Continuous variable
Total Cholesterol	
HDL cholesterol	
Blood pressure	
Smoking	Dichotomous variable
Diabetes	
Left ventricular hypertrophy	

In view of increased baseline risk in different ethnic population a modification of cut offs were suggested (Scott M. Grundy, 1999).

The British Cardiac Society, British Diabetic Association, British Hyperlipidaemia Association together formed the Joint British Society (JBS) for formulating guidelines for primary prevention of CHD. The CHD risk is calculated using the cardiac risk assessor by a computer programme (Durrington, 2000). The calculator is available online on the British heart foundation and British hypertension society website (www.hyp.ac.uk.bhs). The cardiac risk assessment is based on age, gender, systolic BP, diastolic blood pressure, current smoking, diabetes, total cholesterol, HDL cholesterol and electrocardiogram evidence of left ventricular hypertrophy if available. .

Alternatively coronary risk charts may be used. A 10 year risk of CHD event of above 15% is considered increased risk and CHD preventive measures are to be taken in the form of lifestyle modification (primary prevention) or institution of treatment (secondary prevention) (David Wood, 1998).

The Score CHD risk estimation model is based on age, gender, smoking habit, systolic blood pressure, either total cholesterol or TC / HDL ratio and predicts the risk of a fatal CHD event (Conroy RM, 2003). The current EULAR recommendations for CV risk management in RA and other inflammatory arthritis suggests using this model (Peters et al., 2010).

The Reynolds risk score is based on age, gender, smoking, systolic blood pressure, Total Cholesterol, HDL Chol, hs CRP and parental history of CVD before the age of sixty (Ridker et al., 2007, Ridker et al., 2008). This score was derived from participants who were physicians and health professionals and may not represent the general population.

For ethnic minorities especially individuals from individuals from Indian subcontinent it is estimated that the CV risk is higher than predicted and a multiplication factor of 1.4-1.5 may be used. The Ethrisk calculator for British black and minority ethnic groups had been developed based on the Framingham risk calculator (Brindle et al., 2006).

The latest addition to the CV risk estimation scores is the QRISK score which was based on observational data collected in the UK (Hippisley-Cox et al., 2010). This risk calculation includes socioeconomic status, ethnic origin and presence of RA as potential risk modifiers used to estimate CHD risk.

2.11 RA disease activity and CVD

Chronic inflammation in RA is evidenced by raised inflammatory markers namely ESR and CRP which are known to predict CVD (Wallberg-Jonsson et al., 1999).

2.11.1 C reactive protein

C reactive protein (CRP) is an important inflammatory marker secreted by the hepatocytes in response to stimulation by cytokines. It was originally isolated in 1930 as a protein binding to the C polysaccharide in the cell wall of pneumococci (Tillett and Francis, 1930). It is involved in all steps of atherogenesis including initiation, progression and destabilization of a atheromatous lesion (Ross, 1999).

In the women's health study CRP was found to be a strong predictor of future CV event in the general population (Ridker, 2002). Del Rincon et al reported that raised levels of inflammatory markers such as ESR and CRP in patients with RA and general population had an association with raised carotid intima media thickness and carotid plaque. This association was signification after adjusting for CV risk factors (Del Rincon et al., 2003). The Rochester study in RA patients has demonstrated that raised

ESR at baseline is predictive of future CV mortality in an inception cohort followed for fifteen years (Maradit-Kremers et al., 2005). CRP values at baseline in patients with new onset arthritis were found to be important in predicting death from CVD, thereby confirming the role of CRP (Goodson et al., 2005b).

Raised levels of CRP have been observed in obesity and metabolic syndrome as discussed in this chapter section 2.8. As the CRP production is from the liver an additional role of CRP in dyslipidaemia can be considered.

In active RA pro inflammatory cytokines such as tumour necrosis factor alpha (TNF), interleukin 1 β and interleukin 6 are released in systemic circulation from the synovial tissue. The cytokines are able to affect the vascular endothelium and result in endothelial dysfunction and promote premature atherosclerosis by various mechanisms (Sattar et al., 2003). The factors causing atherosclerosis in autoimmune rheumatic diseases are age, gender, hypertension, diabetes, metabolic syndrome, hyperlipidaemia, active disease, use of glucocorticosteroid (GCS) of more than 7.5 mg/day and high cumulative dose and biomarkers such as ESR, CRP, pro inflammatory HDL, oxidized LDL and hyper homocystinaemia (Bevra H. Hahn, 2007). The chronic inflammation may result in progression of atherosclerosis (Maradit-Kremers et al., 2005). Markers of inflammation including high levels of CRP are associated with sub clinical atherosclerosis in RA which can be determined by arterial wall thickening, stiffness and reduced flow mediated dilatation (del Rincon et al., 2005, Nagata-Sakurai M, 2003). Systemic inflammation and traditional CV risk factors together play a role in the

development of atherosclerosis (del Rincón I, 2007). RA patients have a threefold increased incidence of carotid plaque when compared to matched controls (Roman et al., 2006). Active disease, long disease duration, presence of extra articular manifestations are associated with greater carotid intima media thickness (Targonska-Stepniak et al., 2011). In addition patients having a positive rheumatoid factor (RF) and high disease activity represented by a disease activity score (DAS) 28 of more than 5.1 was associated with increased mortality (Mikuls et al., 2011).

The therapeutic considerations suggested are to aggressively control disease activity by using treatments known to affect atherosclerosis such as methotrexate, hydroxychloroquine, treat hypertension, diabetes, obesity, dyslipidaemia and use anti platelet agents or anticoagulants when required (Bevra H. Hahn, 2007).

In a study in 19 South Asian Indian RA patients sub clinical atherosclerosis was found in one third of the participants and age and tender joint count were independent predictors of abnormal carotid intima media thickness (CIMT) (Grover et al., 2006). This study was followed by another larger case control study addressing atherosclerosis in RA and found CIMT was significantly higher in RA when compared to matched controls (Mahajan et al., 2008). Plaques were observed in 21% of the participants. The patients in both the studies were young (less than 45 years). However, these two studies excluded patients with known traditional risk factors. The second study had patients with longer disease duration (12 years). The prevalence of atherosclerosis in this young

RA cohort in the presence of factors associated with development of atherosclerosis especially diabetes is still unknown.

2.12 Medication used in the treatment of RA and the risk of CVD

The medicines used in treatment of RA may positively or negatively affect the CV risks. Use of disease modifying anti rheumatoid drugs (DMARDs) may positively affect the CV risk by reducing inflammation. The role of corticosteroids and NSAIDS are controversial.

2.12.1 Non steroidal anti inflammatory drugs

Non steroidal anti-inflammatory drugs (NSAIDs) are associated with increased CV events in the general population (Hippisley-Cox J, 2005, Chan, 2006). The NSAIDs used for pain reduction in arthritis are classical NSAIDs that non selectively block cyclo- oxygenase (COX) 1 and 2 and selective inhibit COX 2. NSAIDs in general are known to be associated with salt and water retention resulting in peripheral oedema and weight gain, increased blood pressure and worsening of heart failure (Burnier, 2006, Gys`ele S. Bleumink, 2003). Traditional NSAID naproxen was found to decrease the risk of CVD by sustained inhibition of platelet aggregation by inhibiting COX 1 mediated thromboxane (Capone ML, 2004). This effect may be cardioprotective (Daniel H. Solomon, 2003). The anti- inflammatory effect of NSAIDs may reduce inflammation and be beneficial in atherosclerosis (Ray Wa, 2002). In a study of a cohort of new onset arthritis followed for ten years, NSAID use was not found to be associated with excess CV mortality (Goodson et al., 2009).

2.12.2 Glucocorticosteroids

The role of glucocorticosteroids (GCS) is controversial. Glucocorticosteroid use was associated with fluid retention, hypertension, osteoporosis and impaired glucose tolerance resulting in diabetes (Andrews and Walker, 1999, Whitworth et al., 2000).

However, use of these drugs to suppress disease activity in RA, may increase physical activity levels as well as reducing systemic inflammation. With regard to the cardiovascular system, the dose of glucocorticosteroids may be important. In a study by Toms et al, in RA patients, low (<7.5mg/day) and medium dose (>7.5 mg/day) prednisolone use were not associated with metabolic syndrome, hypertension or lipid abnormalities. The authors concluded that this could be due to beneficial effects of steroids in suppressing inflammation (Toms et al., 2008). Therefore, whilst it is likely that glucocorticoids influence CV risk factors, their effective suppression of disease activity in RA may lead to a neutral effect on CVD events in RA. GCS were found to be effective in relieving signs and symptoms of RA as monotherapy and in combination of DMARDs (Gorter et al., 2010). A review article demonstrated a poor association between exposure to low dose GCS and CV risk factors but a trend for increased CV events (Adeline Ruyssen-Witranda, 2011).

2.12.3 Disease modifying anti rheumatic drugs

2.12.3.1 Traditional DMARDs

Disease modifying anti rheumatoid drugs (DMARDs) may reduce disease activity thereby reducing CV risk. Studies have reported reduced CVD events in patients using DMARDs (Suissa et al., 2006, Naranjo et al., 2008). The most widely studied drug is

methotrexate. Previously it was thought that this drug may increase CV risk by increasing homocystine but concomitant use of folic acid reduced this effect (Eikelboom JW, 1999, Slot, 2002, Desouza C, 2002). However in a study assessing mortality in patients with RA, use of methotrexate was found to be associated with a 70% reduction in CV related mortality compared to other DMARDs (Choi et al., 2002). Methotrexate was not found to be associated with increased risk of CVD on long term use (C Salliot, 2009). A systematic review has reported that methotrexate use is associated with reduced CVD events and CVD mortality (Westlake et al., 2010).

Leflunomide use was reported to increase blood pressure and adversely affect the CV risk (Solomon et al., 2006, Rozman et al., 2002, Smolen et al., 1999). There are reports of leflunomide lowering blood glucose and decreasing body weight (Coblyn JS, 2001, Young Hee Rho, 2009).

Hydroxychloroquine use is associated with having benefits on the CV risk in RA by improving the lipid profile (M, 1996). It is also known to reduce the risk of developing diabetes (Bili et al., 2011) reducing blood pressure (Rho et al., 2009).

Sulphasalazine has not been much studied in the context of its effect on CV risk. There is a suggestion that this drug may be associated with a reduction in CVD (van Halm et al., 2006). A report has suggested cardioprotective effect by reducing platelet reactivity (MacMullan PA, 2008).

2.12.3.2 Biologic DMARDs

Tumour necrosis factor (TNF) alpha may improve insulin sensitivity (Huvers FC, 2007). These drugs also reduce CVD but the effect was not found to be as consistent as methotrexate (Westlake et al., 2011). Studies have looked at the effect of these drugs on lipid profile, some have reported no effect on lipid profile (Soubrier et al., 2008) and others have found an increase in HDL (Popa et al., 2005, Spanakis et al., 2006) and total cholesterol but the atherogenic index was the same (Schimmel EK, 2009) while others found the effect was found to be for a short term (Hurlimann et al., 2002, Dixon and Symmons, 2007). Lower incidence of first CV event has been reported (Jacobsson, 2005). Longer exposure to TNF alpha drugs was associated with a lower risk of CV events (Naranjo et al., 2008).

2.13 Statins

Statins are hydroxyl methylglutaryl coenzyme A (HMG co A) reductase inhibitors which inhibit cholesterol biosynthesis pathway (Buhaescu and Izzedine, 2007). There is evidence that statins have a role beyond their cholesterol lowering property and are believed to exhibit "pleotropic effects"(Almuti et al., 2006, Liao, 2005). Statins decrease vascular inflammation, improve endothelial cell function, decrease platelet activation and aggregation, decrease vascular smooth muscle cell proliferation and migration and also stabilize the atherosclerotic plaque (Sadowitz et al., 2010). In a randomised control study of statin looking at cardiovascular events in individuals with normal LDL but high CRP found that patients treated with statins had a 37% lower CRP levels (Ridker, 2003). In addition to their use in dyslipidaemia statins are used in

prevention of CHD, stroke and peripheral arterial disease. Statin use in RA is associated with reduction of CV risk factors, disease activity and progression (Nurmohamed and Dijkmans, 2009, Gazi et al., 2007). There are reports of reduction of ESR, CRP and other disease activity parameters with the use of statins in patients with RA (McCarey et al., 2004). Statin use is also associated with reduced risk of development of RA in patients with hyperlipidaemia(van Halm VP, 2007). The EULAR recommends statin use as a preferred treatment option in RA due to their potential anti inflammatory effects (Peters et al., 2010).

2.14 Burden of cardiovascular disease in South Asian Indians

The prevalence of CVD is high in South Asian Indians and occurs almost a decade earlier when compared to Caucasians (Salim Yusuf and John Varigos, 2004, Teoh, 2007). Traditional CV risk factors are more prevalent in this population (Enas et al., 1992). The risk of CVD is ten times higher in individuals less than 40 years (Enas et al., 1992, Enas, 2000).

A study in UK has demonstrated a 50% increase in CV mortality when south Asian migrants were compared to the general host population (McKeigue PM, 1989). There are studies in South Asians who have migrated to different countries (Anand et al., 2000, Enas et al., 1997, Misra, 2010, Venkataraman R, 2004, S.S. Liem, 2009).These studies have shown a marked increased prevalence of traditional CV risk factors in the migrant Indian populations when compared to the country of their residence.

Indians residing in India have a very high prevalence of traditional CV risk factors. Prevalence of metabolic syndrome is high and is seen in 25 – 30 % of adult South Asian Indians (Misra A, 2006). In India, there are additional, geographical variations in CV risk. Urban Indians have increased risk when compared to rural inhabitants (Mohan et al., 2001). South Indians have been reported to have an increased prevalence of CV risk factors compared to North Indians (Begom R, 1995). The WHO project on sentinel surveillance of Indian industrial populations has demonstrated that in India the highest prevalence of obesity and a high waist circumference is observed in Hyderabad, Andhra Pradesh. (Reddy et al., 2002).

Due to the increased prevalence of CV risk factors and increased CVD prevalence observed, South Asian ethnicity may be considered an independent risk factor for CVD (Milan Gupta 2006). Recognition of this strong association with CVD has led to incorporation of ethnicity into more recent CV risk prediction tools.

In summary, there is substantial literature demonstrating that RA is associated with increased CVD and this is partly due to an increase in CV risk factor prevalence. The South Asian population is at increased risk of CVD events and this population has greatly increased CV risk factors associated with the metabolic syndrome. What is not clear from the current reported literature is whether South Asian Indian subjects who develop RA are at further increased risk of CVD.

Chapter 3 - Aims and Objectives

3.1 Aims

The main aim of this thesis is to measure the prevalence of traditional risk factors for CVD in urban Indian patients (Hyderabad, Andhra Pradesh) with rheumatoid arthritis (RA) and to compare these risk factors with age and gender matched normal controls from a similar geographic location. The effect of treatment by biologic disease modifying anti rheumatoid drugs (DMARDs), Etanercept and newer traditional DMARD Leflunomide on the traditional CV risk factors are also studied.

3.2 Objectives

3.2.1 Prevalence of traditional CV risk factors

1. To report the prevalence of traditional CV risk factors in consecutive South Asian Indian RA patients.
2. To explore the prevalence of CV risk factors in RA patients stratified by gender and rheumatoid factor status.
3. To compare the prevalence of traditional CV risk factors in patients with RA and age and gender matched controls free from inflammatory arthritis.
4. To evaluate the elevated CV risk factors and composite 10 year risk of coronary heart disease (CHD) in RA patients and controls.
5. To examine whether the ten year risk of CHD in patients with RA is associated with disease activity score (DAS 28).
6. To ascertain whether this research can form a basis for better identification of CV risks in Indian patients with RA.

Effect of treatment with leflunomide on CV risk factors – Sub group analysis

7. To determine whether 10mg/day leflunomide therapy in patients with active RA results in rise in blood pressure and CV risk.
8. To explore if leflunomide use is associated with modification of lipids, body mass index and fasting blood glucose.

Effect of treatment with biologic response modifier Etanercept on CV risk factors – Sub group analysis

9. To determine if treatment with a short course of TNF alpha inhibitor Etanercept influences CV risk factors in patients with active RA after etanercept is withdrawn.
10. To explore if any long term effect on CV risk factors is observed six months after etanercept is withdrawn.

Overall this research for studying traditional CVD risks factors in RA patients from Hyderabad is aimed to address

- The need to undertake research in a population which does not have enough published data.
- Day to day available simple cost effective techniques can be applied in patient assessments to generate scientific data.
- By using patient-friendly methods an attempt is made to allow research to percolate to the understanding of general and lay populations without altering the comfort and security level of the participants.
- This work should benefit from the latest research methodologies used in the United Kingdom that are applied to patient population in Hyderabad India collected under a single organization.

Chapter 4 – Methods

4.1 Introduction

In this chapter the study populations of patients and controls are described. The methodology and data collection for CV risk assessment are described in detail. Data collection of each study included in this thesis is discussed. Patient evaluation is described in detail. The methods used to measure cardiovascular risk are described.

4.2 Study location

The RA patients were recruited from rheumatology clinics conducted at the Sri Deepti Rheumatology Centre (SDRC) in Hyderabad, Andhra Pradesh (AP), south India.

Patient evaluation was done at SDRC as it is located in central Hyderabad and is well connected to surrounding areas. The SDRC is a tertiary care centre which caters to patients with rheumatological problems in Hyderabad and surrounding districts (Figure 4.1) and has one of the largest patient populations in AP. The patients seen are largely from middle and upper middle class families. RA accounts for 30-35% of rheumatological conditions treated at this centre. Most patients attending this rheumatology service are from an urban population. SDRC is an out- patient referral centre.

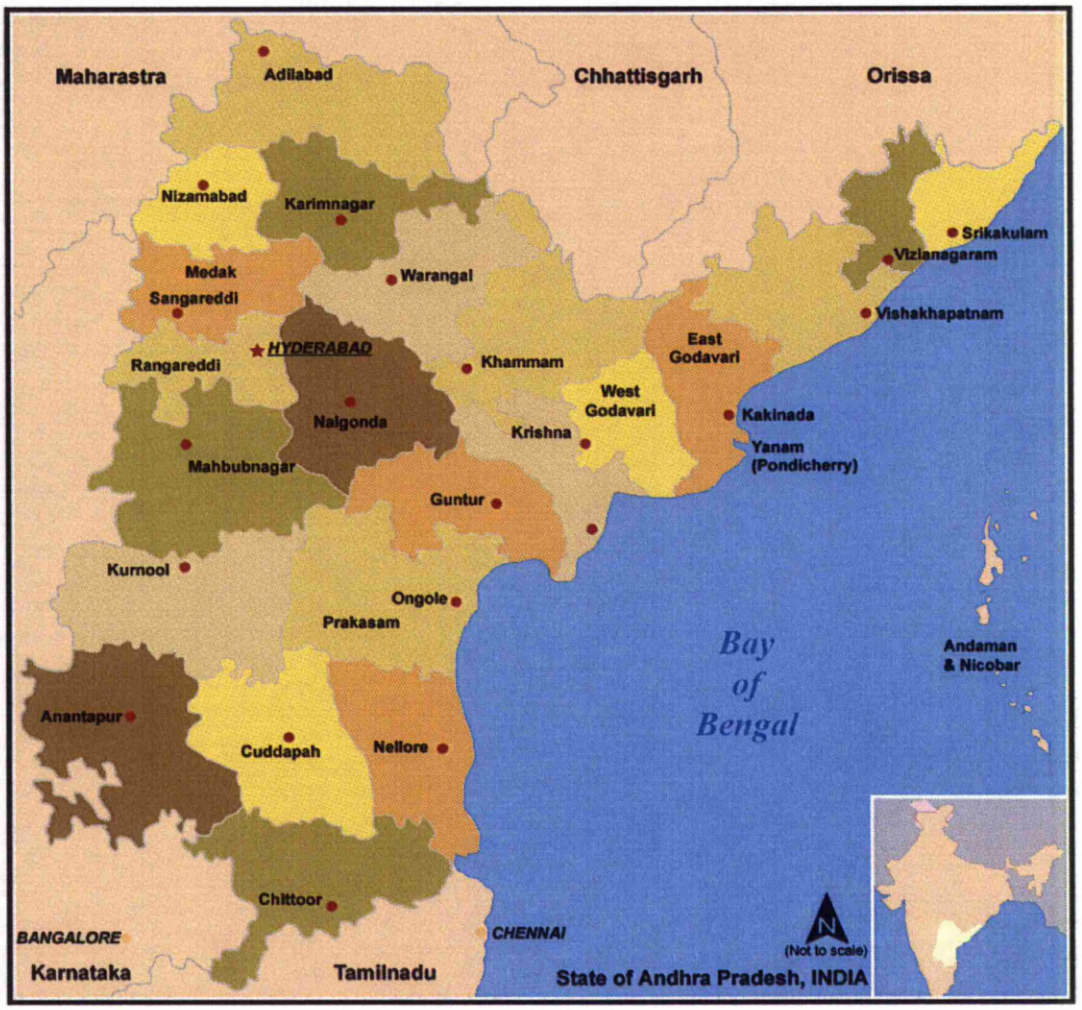
The SDRC is staffed by 2 rheumatologists and 2 general medical interns. There are onsite biochemistry and pathology services as well as in-house radiology, phlebotomy,

physiotherapy and pharmacy. The chief Rheumatologist and director of SDRC is Dr Uppuluri Ramakrishna Rao (URKR).

4.3 Timeline

The studies for the thesis were conducted between July 2005 and June 2009. The first group of studies: 1) exploring the prevalence of CV risk factors in an RA cohort, 2) exploring whether CV risk factors are more prevalent in RA cases compared to population controls, and 3) exploring whether CV risk factors are associated with high disease activity in RA, recruited study participants between July 2005 and October 2008. The second group of studies identifying whether use of: 1) leflunomide and 2) etanercept influenced the prevalence of CV risk factors, recruited study participants between December 2006 and June 2009. The patients were evaluated before and after initiating such therapy.

Figure 4.1 Map of Andhra Pradesh



Hyderabad is the capital district of A P and has an estimated population of over 7 million (2008) spread across 6,300 Km square. The city has a cosmopolitan population with people of different religions and languages.

4.4 Study designs and patient populations

4.4.1 Prevalence of CV risk factors in RA

The prevalence of CV risk factors was an observational cross-sectional study describing the prevalence of CV risk factors in a cohort of unselected RA patients attending the SDRC for routine rheumatology care.

4.4.2 Comparing CV risk factor prevalence in RA cases with controls

This cross-sectional observational study used a case control design to explore whether CV risk factors were more prevalent in RA cases compared to local controls, free from inflammatory joint disease, and frequency matched for age and gender to the cases. The RA cases were the same patients examined and described as the RA cohort.

4.4.3 Disease activity and CV risk study

This observational cross-sectional study used the RA cohort and stratified them into two groups based on their disease activity. The CV risk profile was compared between the group of patients with high disease activity (defined as DAS28 >5.1) and those with low/moderate disease activity.

4.4.4 The influence of drug treatment on CV risk studies

The drug treatment studies were longitudinal studies, exploring the influence of drug treatment on CV risk. Patients who had active RA and were keen to start either leflunomide or etanercept were studied. This was an open label study and the patients

and individuals assessing them were aware of the drug there were taking. Cost of the drug treatment was paid by the patient. As this is in accordance with the routine clinical practice any bias in patient evaluation was not foreseen. Patients were assessed prior to starting leflunomide and were reassessed after leflunomide treatment was established. For the etanercept study, patients were assessed prior to starting etanercept. The same patients were reassessed after etanercept had been withdrawn. The detailed methods for the treatment exposures are discussed in more detail in the relevant chapters.

4.5 Ethical approval

The study proposals and protocols were presented to the institutional ethics committee of SDRC by Firdaus Fatima (FF). The ethics committee of SDRC operates as per good clinical practice (GCP) guidelines. Ethical approval for all the studies included in this thesis was obtained by the institutional ethical committee of SDRC, and an informed consent from all the subjects was taken. Literate subjects gave a written consent and the individuals who could not read and write gave a witnessed thumb impression. The consent procedure was conducted by FF.

4.6 Eligibility criteria

All subjects taking part in the study were above 18 years of age. RA patients fulfilled ACR 1987 classification criteria. Subjects who did not report a psychiatric illness and were able to give informed consent were included. Subjects with known CVD on treatment were excluded. Known subjects with dyslipidaemia on lipid lowering agents

were not included. All participants were South Asian Indians and no other ethnic groups were included in either the cases or control groups.

The inclusion and exclusion criteria are described in Table 4.1. When the subject was found to be eligible for inclusion to a study they were provided information about the study and informed consent was obtained. After consent was obtained subjects were then evaluated by a systematic interview as mentioned in the baseline assessments (Section 4.8), by one of the trained physiotherapists.

Table 4.1 Eligibility criteria for enrolment of subjects

Inclusion criteria

1. All subjects above 18 years
2. Willing to give informed consent
3. Fulfilling ACR 1987 classification criteria (RA cases)

Exclusion criteria

1. Known CVD on treatment
2. Known dyslipidaemia on lipid lowering agents
3. History of stroke, cancer, significant hepatic or renal abnormality
4. Joint deformity causing difficulty in anthropometric measurements
5. Inability to give consent
6. Presence of known inflammatory joint disease (For control subjects)

4.7 Selection of RA patients

Consecutive RA patients from rheumatology out-patient at SDRC were identified The ACR criteria (Arnett et al., 1988) were applied to all cases enrolled in the study. When

patient fulfilled four out of seven ACR criteria they were included. The significance of the CV risk assessment was explained to patients.

4.8 Selection of controls

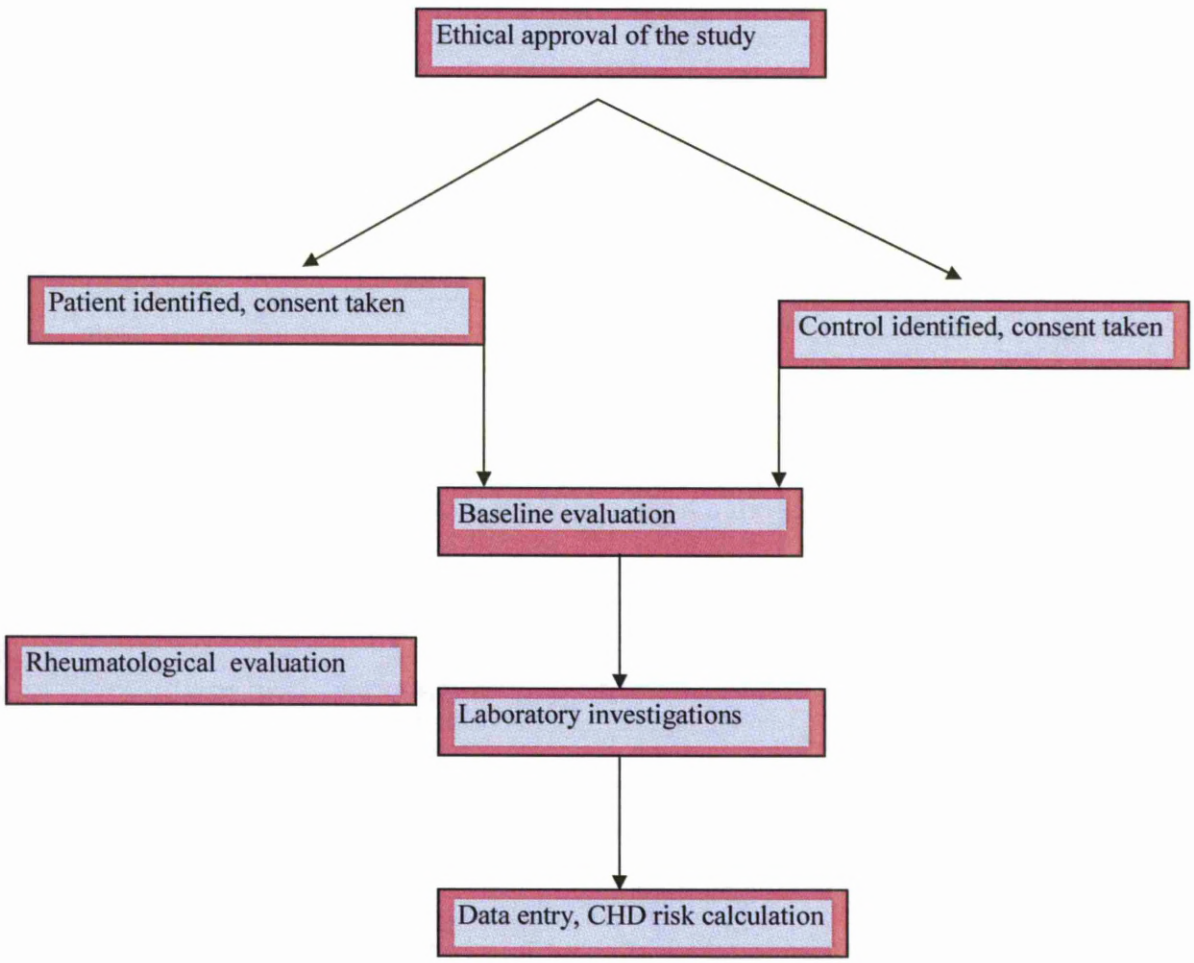
Control patients who were free from inflammatory arthritis were recruited in the study. These were frequency matched for age and gender to the cases. The RA cases were encouraged to recommend friends and relatives to take part in the control group for this study. This allowed a degree of matching for both social class and urban dwelling of participants, as the index case of RA was likely to recommend friends or relatives from a similar background to take part in the study. One fourth of the control group participants were hospital staff and their relatives. These controls were from middle and upper middle class families and were from a similar background to the RA cases. To ensure that controls were from a similar background to the cases caution was taken not to enrol class four employees and their relatives (sweepers, cleaners, drivers etc). The controls were given separate appointments for assessments.

4.9 Baseline assessments of study participants

The inclusion and exclusion criteria were applied to all patients and controls (Table 4.1). Informed consent was taken by FF. The subjects underwent a detailed assessment for the occurrence of traditional CV risk factors. The RA patients were called cases and the matched individuals are referred to as controls. While addressing patients and controls together they are referred to as subjects.

The initial history and data collection was done by one of the four physiotherapists who have similar training. All the physiotherapists included in patient data collection had completed their bachelors in physiotherapy and were taking patient history for the past one year. Further training in patient data collection and anthropometric measurements was given by FF. After consent the subjects were taken to an examining room and made to sit comfortably in a chair. Full details and the scheme of analysis corresponding to chronological sequence is outlined see Figure 4.2. The data obtained was recorded in paper case record forms (CRF).

Figure 4.2 Flow chart of study procedures



Blood pressure (BP) recording for each patient was done three times in the right upper arm in sitting position. The three readings were taken by the same person using same mercury sphygmomanometer (Diamond regular (IS3390) Mfg in India). The sphygmomanometer was placed at the level of the heart. The BP reading was recorded to nearest 2 mm. Three readings were taken i.e. (1) before detailed history (2) after history (3) after anthropometric measurements. The timing for BP record was adjusted for all patients such that the first recording was after sitting for fifteen minutes, and repeated twice after ten minutes intervals. The mean of 3 readings was calculated and entered on the paper CRF.

The evaluation process consisted of entering the subjects name, age and gender on the CRF. The subject's initials were also entered. In the subjects who were unable to give their exact age then the date of birth was estimated by writing the month and date as first January, the year of birth was calculated from the age at which a major life event occurred (marriage, birth, death of a family member or a major calamity) and year of birth was retrospectively calculated from the year of evaluation. Eg if the subject was married at 18 years of age and was married for the past twenty years then the age of the subject was entered as 38 years.

A detailed family history including the presence of co morbidities in the family was taken. History of CVD was considered when a member of the family (first degree relative) was diagnosed to have CVD before the age of 55 years for males and before the age of 65 for females (NCEP, 2001).

The subject's personal details including history of co morbidities, history of smoking and diet (Vegetarian) was taken. The co morbidities, recorded systematically, included hypertension (HTN), Diabetes mellitus (DM), CVD and hypothyroidism. The co morbidities were classified as being present if the subject reported prior diagnosis by a physician or if the subject was taking prescription medicines prescribed for treatment of a co morbid condition and the indication was written in the medical records. Review of current medication was used to validate current co morbid diagnoses. Subjects with known CVD on treatment were excluded. Very few individuals who did not have a documented evidence of CVD and were not on any treatment for it but reported an anecdotal history of CVD were not excluded.

Smoking history was taken and the subjects were classified as smokers and non smokers. Subjects who were ex smokers for more than a year were considered as non smokers. Details about vegetarian diet were enquired and if the subject was a vegetarian the entry was made as yes and no for non vegetarians respectively.

For RA patients, the duration of disease is determined by the duration of symptoms of RA in years. A detailed history of medicines used by patient at the time of evaluation was taken. The history comprised the use of medicines for co morbidity and treatment of RA. The RA specific drug history included the use of NSAIDs, glucocorticosteroids (GCS), and disease modifying drugs including biologic response modifiers.

4.10 Anthropometric measurements

The anthropometric measurements included weight, height, waist and hip measurements. Weight was measured in kilograms using a digital weighing machine which was calibrated (Krups Mfg in India). The weight was recorded in minimum clothing without footwear, the subject was asked to keep the purse aside and empty pockets, when applicable, before climbing on the weighing machine. The subject was asked to look straight ahead whilst the weight was recorded. Two reading were taken one after another. Average of the two readings was taken and a value close to the nearest gram was entered.

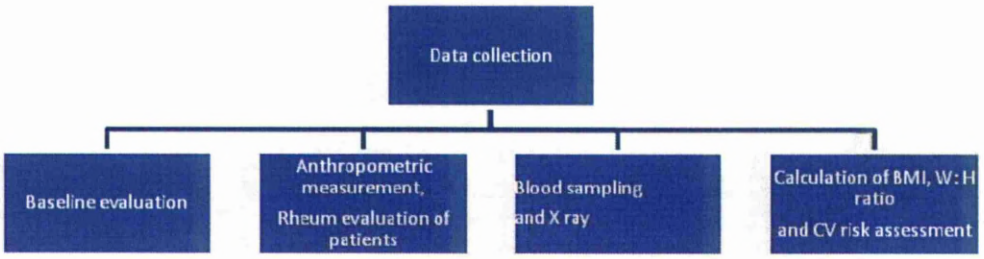
Height was measured in centimetres. The subject was asked to remove footwear and stand close to a wall in such a way that the head, buttocks and heels were touching the wall. Height was measured using a wall mounted height measuring tape (WSO45 Narang medical limited). The height was entered to the nearest centimetre. Using a measuring tape waist and hip measurements were taken. The subject was asked to stand straight with feet close and the waist measurement was taken at a level midway between the lowest rib and the iliac crest. The hip measurement was taken at the widest area of the buttocks. The readings were recorded in centimetres and a value corresponding to the nearest centimetre was entered. The subject was then referred to URKR / FF for physical examination. The schematic representation of the study is given in figure 4.2.

4.11 Physical and rheumatological evaluation

Detailed physical examination was done either by URKR or FF. Twenty eight joints were examined for swelling and tenderness in RA patients. A joint with soft tissue swelling which could also be detected by manual palpation was considered as swollen joint. Tenderness of the joint was elicited as pain on applying firm pressure on the joint in such a way that there was blanching of the examiners nail bed of the thumb and index fingers. The joints examined include bilateral shoulders, elbows, wrists, first to fifth metacarpophalangeal joints (MCP), thumb interphalangeal and second to fifth proximal interphalangeal joints (PIP), right and left knee joints. The 28 joint count was done to calculate the disease activity score (DAS 28) which is validated for measuring disease activity (Prevoo ML et al 1995).

The patient's global assessment of disease activity was done by asking the patient to mark on a numeric scale of 100 mm (visual analogue scale - VAS). No disease activity was marked as '0' and 100 for highest activity possible. The patient record was checked for the presence of rheumatoid factor and if the RF was done within six months it was not repeated. A chest X- ray was taken in subjects who had not had such imaging within the prior three months. Later the subject was sent to the in-house laboratory for blood sampling. The scheme of data collection is given in figure 4.3. The paper CRF was checked by FF for any missing data. Later the patient details were transferred to a Microsoft excel spreadsheet by FF.

Figure 4.3 Scheme of data collection



4.12. Laboratory investigations

4.12.1 Blood samples and test methods

A requisition for investigations was given to the subject. Random blood sample was collected in the laboratory. The blood tests requested were full blood count (FBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), total lipid profile including total cholesterol (T-Chol), triglycerides (TG) and high density lipoprotein (HDL-Chol) cholesterol, thyroid profile was done in subjects who were not hypothyroid but have a clinical suspicion of hypothyroidism and do not have a latest thyroid profile. Routine liver and kidney function tests were also performed. A random blood sample was taken from the patient. Analysis of the sample collected was done at the in-house laboratory on the same day using fresh serum samples. Blood sampling was done by one of the phlebotomist and the sample was drawn mostly from the left median cubital vein and a unique numbering system was used for all containers in which the sample

was collected. The same number was used for urine sample containers also. The containers were shifted from the sample collection room on the ground floor to the laboratory situated on the first floor.

The patient's blood sample was collected and serum separated by centrifugation using a semi automated centrifuge. A whole blood sample was also collected in ethylenediaminetetraacetic acid (EDTA). ESR was done by Wintergreen method. T-Chol, serum Triglyceride, HDL-Chol was estimated using reagent and standard from Bio Systems reagents and instruments Costa Brava Barcelona Spain. LDL-Cholesterol (LDL-Chol) was calculated using Friedwalds formula in all subjects (Friedewald, 1972) RF and CRP were done by latex agglutination method (Beacon diagnostics India). The test serum was mixed with CRP latex reagent and if CRP concentration was greater than 6 mg/ml a visible agglutination was observed. A CRP concentration of less than 6 does not show agglutination on the slide. The concentration of the CRP was calculated by the formula CRP (mg/ml) = 6 x D .D was the highest dilution of serum showing agglutination and 6 was the sensitivity in mg/ml. Due to cost limitation a dilution beyond 96 mg/dl was not done in all subjects. RF was also done by agglutination method and the value was calculated by the formula RF IU/ ml=8 x D.

Thyroid profile was done by reagents supplied by Monobind Inc USA. Urine examination was done for all subjects. Fasting venous blood was collected the next day to assess the fasting blood glucose by using the reagent kit obtained from Beacon diagnostics India.

4.12.2 Radiology

Radiographs were routinely done for all patients to look for involvement of joints due to RA. X- ray chest was also routinely done in patients. For subjects included in the study a history of latest chest radiograph was enquired and if the subject did not have a recent chest radiograph then a requisition was given and the subject was asked to have a chest X ray. This was done to rule out any infection, particularly tuberculosis (TB), which may give a positive CRP value or elevation in ESR level. South East Asians have high occurrence of tuberculosis, 4.97 million TB cases have been identified which is more than one third of the global burden and India alone has more than 20% of cases (WHO, 2011). Average prevalence of all forms of TB in Indians is 5.05 per thousand annually (Chakraborty, 2004).

All patients attending SDRC get a baseline hand and feet radiograph as a routine procedure and their record was checked for radiological evidence of erosions to classify them as per the ACR criteria see table 1.2 chapter 1. Repeat X-ray hand and feet was not performed as it would not affect the outcome of the study and also to avoid radiation exposure to the participants.

The radiographs are performed at the in-house radiology department and the radiographs of all the subjects were examined and recorded by URKR before dispensing the X-ray films to the patients.

4.12.3 Reporting the results of investigations

The results of blood reports were entered in the main register. The patient was asked to report the next day after an overnight fast and blood sample was collected for fasting blood sugar (FBS). The blood reports of the previous day were reviewed by URKR/FF and handed over to the patient. Patients having abnormal lipids and elevated/high 10 year risk of CHD events were advised lifestyle modification including diet. These patients were further advised repeat lipid profile estimation and were counselled regarding continuing their medication regularly and keep their disease activity under control.

The subject was told that the report of the FBS would be informed by telephone. If the value was high the patient was asked to come and collect the report and consult their respective physician. The blood reports of the subject were entered in the paper CRF by one of the physiotherapists. All the entered patient data was again checked by FF. The twenty eight joint disease activity score (DAS 28) was calculated by FF with a DAS calculator by entering the values of TJC, SJC, VAS and ESR.

4.13 Data entry

The patient's data were transferred from paper CRF to Microsoft® Office Excel 2003 spread sheet prepared by FF. The patient confidentiality was maintained when analyzing the data by giving each subject a unique identification number (ID) described in Table 4.2. The example cited in the table is hypothetical and does not reveal the data of any patient.

Table 4.2 Identification codes for subjects

Patient name	Mrs D. Lalitha Kumari
Patient initials	DLT
Patient ID code	101
Control ID code	1001 (if DLT was a control)

Table 4.3 Entry of variables

Presence of the parameter	1
Absence of the parameter	0

Eg. If the subject was a female the information was entered in the gender column as 1. In case of males the information was entered as 0. For vegetarian subjects the entry was 1 and 0 for non vegetarian (Table 4.3).

To validate the entered data a check for proper entry and missed data was done after every 10 entries by a review of entered data compared to paper CRF. A sample of the parameters entered was given in Table 4.4. All data was entered in numerical.

Table 4.4 Sample of parameters entered

Code, Case,
Personal details
Initials, Age, Gender, old case, Vegetarian, Smoking
Co Morbidities
Family history (n), DM, HTN, CVD, Co morbidity (n), DM, HTN, CVD, Hypothyroidism
Evaluations
Waist(cm), Hip(cm), Height (cm), Weight (Kg), mean of Systolic BP, Diastolic BP
Calculations
W:H ratio, BMI, CVD risk systolic, CVD risk diastolic
Drug history
NSAIDs, Steroids, Methotrexate (Mtx), Leflunomide(Lef), Sulphasalazine (Ssz), Hydroxychloroquine (Hcq), Etanercept
Lab data
CRP, FBS, T-Chol, HDL-Chol, LDL-Chol, Triglycerides, T-Chol:HDL-Chol ratio, ESR, RF
RA related data
RA, disease duration (yrs), TJC, SJS, VAS, DAS 28.

4.14 Calculations

The subjects waist hip ratio (Waist: Hip) were calculated from the anthropometric measurements in the paper CRF by dividing the waist measurement value by the hip measurement. The body mass index (BMI) was calculated by dividing the weight in kilograms by height in meters squared. The formulae for auto calculations of Waist:Hip ratio, BMI, and ratio of T-Chol to HDL-Chol were programmed into the Microsoft Excel sheet used for data entry.

DAS 28 was calculated in RA patients by using online DAS 28 calculator by Alfons and Michiel (http://www.das-score.nl/dasculators.xls). The DAS 28 value was obtained by entering four parameters - TJC, SJC, Patient's global assessment of disease activity and ESR. The DAS28 value ranges were from 0 to 10. A value above 5.1 was considered as high disease activity, DAS 28 in the range of 3.2 to 5.1 was moderate disease activity and less than 3.2 was low disease activity (Table 4.5).

Table 4.5 EULAR response criteria (J. Fransen, 2005)

Low DAS	Moderate DAS	High DAS
< 3.2	3.2-≤5.1	>5.1

The T-Chol : HDL-Chol ratio was obtained by dividing the T-Chol value by the HDL value. LDL-Chol value was obtained by using the Friedewald's formula LDL-Chol = T-Chol – HDL-Chol – TG / 5.

4.15 Maintaining the quality of assessments

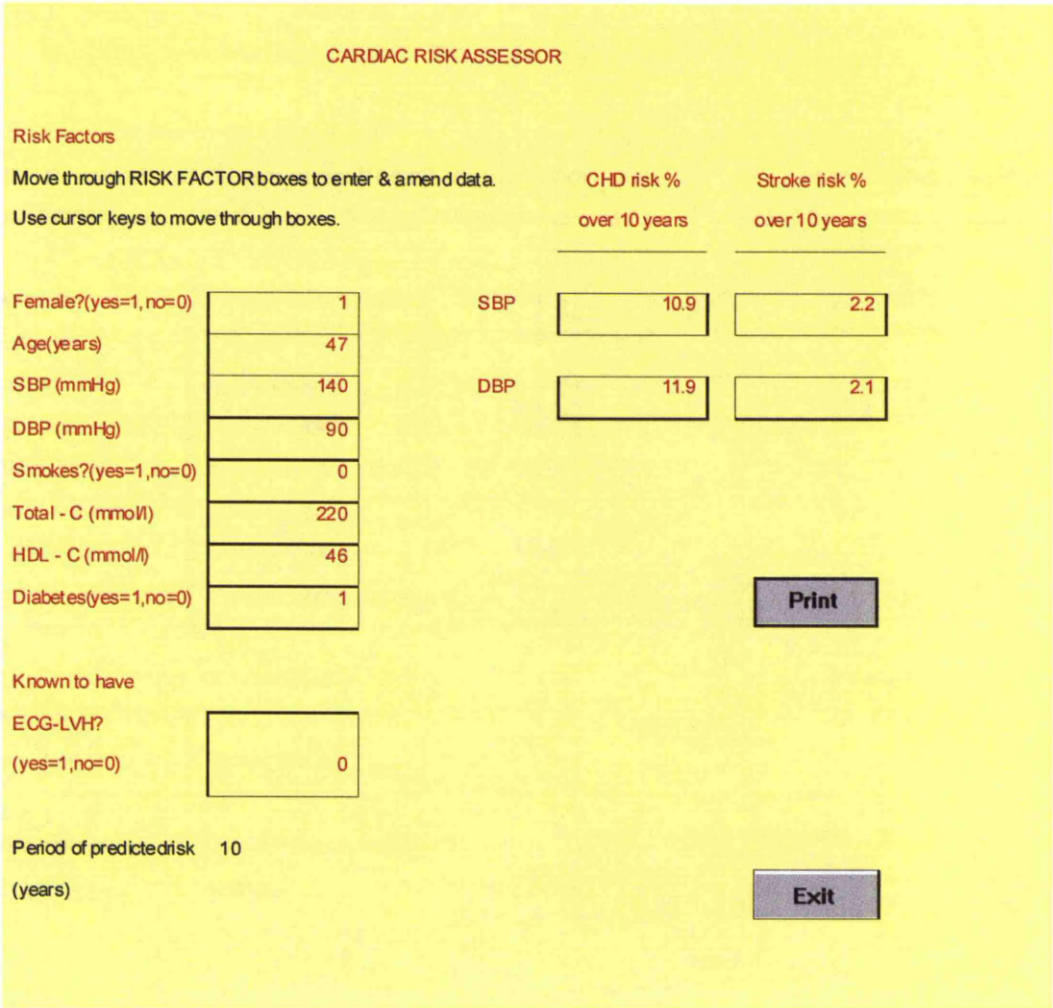
Measures were taken to ensure that the patient recruitment was done as per the inclusion and exclusion criteria. The records of enrolled patients were reviewed randomly by FF to see if all the criteria were fulfilled. The subject evaluation was done by trained physiotherapists who had a similar training. To maintain uniformity in the standard of evaluation the physiotherapists were reassessed periodically by a same subject being evaluated by FF and the CRF was compared for discrepancies. The physiotherapists were also observed assessing patients from time to time.

4.16 Coronary heart disease risk assessment

The composite CV risk score for a 10 year risk for coronary heart disease CHD event was calculated according to Joint British Society (JBS) calculation using the cardiac risk assessor computer program (Durrington, 1997) and the Framingham CHD risk score (Wilson, 1998).

The JBS risk score calculation includes age, gender, systolic BP, diastolic BP, smoking, total cholesterol, HDL cholesterol, diabetes and ECG evidence of LVH (optional). Calculation for a ten year risk of CHD event and stroke is obtained. Risk of stroke is not included in this study. A 10 year CHD risk of more than 10% was considered elevated and a risk of 15% and above was considered high for the study participants. The 10 year risk calculation of a 47 year diabetic female is given in figure 4.4

Figure 4.4 CHD risk calculation



The 10 year risk of a CHD event would be 10.9 % for a female with this risk factor profile. However, if this was repeated for a male participant this would increase to 11.3% and to 17.4% if the male participant was a smoker.

The Framingham 10 year coronary heart disease risk prediction (Wilson, 1998) calculates CHD risk based on measurement of age, gender, total cholesterol, HDL

cholesterol, smoking, diabetes and hypertension. The risk estimates for this risk prediction tool were derived from the Framingham heart study (Dawber, 1980) For the purpose of this study we utilized the "hard" coronary heart disease event prediction, which includes all coronary heart disease events but not development of new diagnosis of angina. This makes it similar to the JBS CHD risk prediction. A risk score of below 10% or less is considered low risk, score between 10-20% is intermediate risk and above 20% is high risk. The Framingham risk scores have been validated in European, African, and Hispanic Americans. (D'Agostino RB Sr, 2001); it has not been validated in Asian Indians. However, Framingham risk prediction tools are used worldwide to assess CV risk and many other risk prediction tools, including JBS, have been developed (Ioanna Tzoulaki, 2009) using data from the Framingham heart study. For the purpose of this study a 10 year Framingham risk score of 10% or more was considered elevated and a score of 15% or more was considered high for the study participants.

4.17 Metabolic Syndrome

Metabolic syndrome is an established risk factor for development of CVD (Peter W.F. Wilson, 2005). Metabolic syndrome was assessed using National Cholesterol Education Programme Adult Treatment Panel III (NCEP- ATP III) (ATPIII, 2002). A subject was classified as meeting the criteria for metabolic syndrome if three out of five criteria were fulfilled see Table 4.6

Table 4.6 Criteria for Metabolic Syndrome

Risk Factor	Cut off point
Waist circumference	>102cm(>40 inches) in males
	> 88cm (>35 inches) in females
Triglycerides	≥150mg / dl
Low HDL	Male < 40mg / dl, Female < 50mg / dl
Blood pressure	>130/85 mm of Hg or an antihypertensive
Fasting blood sugar	>110 mg/dl or diabetes

4.18 Elevated CV risk factors

Continuous CV risk factors were divided into categorical variables. These are summarised in Table 4.7. The elevated CV risk factor categorical variables were used in the analysis of case control study, the high RA disease activity study and the treatment effect studies.

The same CV risk assessments and CHD risk prediction methods were used for all participants involved in the studies presented in this thesis.

Table 4.7 CV risk factor variables defining categorical variables denoting elevated levels for continuous data

CVD Risk factor	Definition	Reference
Systolic hypertension	Systolic BP ≥140 mmHg	(Bryan Williams 2004)
Diastolic hypertension	Diastolic BP ≥ 90 mmHg	
High Waist:Hip ratio	Waist:Hip ratio classified as high if ratio ≥ 0.95 in Women & if ≥1 in Men)	(ATPIII, 2002)
Elevated BMI	BMI>25 WHO definition of overweight/obese compared to normal or underweight BMI	(WHO, 1995)
Elevated T-Chol	T-Chol >200mg/dl	(NCEP, 2001)
Low HDL-chol	HDL-Chol <40mg/dl	
Elevated T-Chol:HDL-Chol ratio	TChol:HDL ratio >4.5	
High triglyceride	TG >150mg/dl	
Elevated FBS	FBS >100mg/dl	(NCEP, 2001)
FBS in Diabetic range	FBS in DM range >126 mg/dl	
Elevated Framingham CHD risk	Framingham CHD risk >10% n (%)	(Peter W. F. Wilson, 1998)
High Framingham CHD risk	Framingham CHD risk >15% n (%)	
Elevated CHD risk score based on systolic BP	JBS CHD risk >10% n (%) (systolic)	(David Wood, 1998)
High CHD risk score based on systolic BP	JBS CHD risk >15% n (%) (systolic)	
Elevated CHD risk score based on diastolic BP	JBS CHD risk >10% n (%) (diastolic)	
High CHD risk score based on diastolic BP	JBS CHD risk >15% n (%) (diastolic)	
Metabolic syndrome	Based on NCEP ATPIII definition	(ATPIII, 2002)

4.19 Statistical analysis

4.19.1 Descriptive statistics

In this thesis, non-parametric methods have been used to describe the data that are not normally distributed. The distribution of values including central tendency and spread

of variables are described using median values and the inter-quartile range [IQR]. For normally distributed data, means and standard deviations are presented. Number and percentage have been used to describe categorical variables.

Comparison of non-parametrically distributed variables between groups was conducted using the Wilcoxon ranksum test (also known as the Mann Whitney U statistic) to explore whether the distribution of the variable was significantly different in two independent populations. For the treatment effect analyses, paired data for each subject was available and the Wilcoxon matched pairs Signed-rank test was used as within patient matching was available. This statistic explores whether the variable distributions between paired observations are the same.

For normally distributed data the students t-test was used and the paired t-test was used to compared matched normally distributed data.

Discrete binomial categorical variables were analysed with Chi Squared test. This allows simple hypothesis testing for differing proportions in each study group.

For the case control study, the controls were selected to provide a similar frequency of gender and age distributions to the cases. It was not practical to perform a matched analysis in this study. Therefore logistic regression was used to explore associations between categorical variables and cases. This analysis was repeated adjusting for age and gender as it was felt that these variables may confound the relationship between CV risk factors and RA. The same methods were employed to analyse the disease activity study and the treatment effect studies.

Chapter 5 – Prevalence of traditional cardiovascular risk factors in rheumatoid arthritis

In this chapter the prevalence of traditional CV risk factors are described and composite CHD risk prediction scores are calculated in a cohort of patients with rheumatoid arthritis. CV risk factor prevalence is compared between male and female RA patients and in rheumatoid factor (RF) stratified subgroups of patients.

5.1 Introduction

Mortality is increased in patients with rheumatoid arthritis (RA). RA patients die early due to cardiovascular disease (CVD), which is mediated by CV risk factors (Wallberg-Jonsson et al., 1997, Symmons et al., 1998). Traditional CV risk factors and RA disease activity markers have been identified as predictors of future CV events (Solomon et al., 2010). Smoking is strongly associated with increase in the CV risk and is also implicated in the development of RA (Goodson, 2002, Heliovaara et al., 1995, Goodson et al., 2004). Increased CV mortality is observed in patients with RA especially in those with a positive rheumatoid factor (RF) (van Schaardenburg D, 1993, Goodson et al., 2002, Gonzalez et al., 2008a). RF is found to have a positive association with diabetes and a negative association with total cholesterol (Tomasson et al., 2010).

There are gender differences in the development of CVD. When compared to men, CVD occurs 10 – 15 years later in women. In premenopausal women the effect of estrogens is thought be cardio protective but the risk of CVD rises after menopause.

This may be in part due to hormonal effects on lipid profiles. Up to puberty the lipid profiles are similar in men and women. After puberty, due to the effect of testosterone, HDL levels drop in males. After menopause the testosterone levels increase, there is increase body weight, decrease in HDL cholesterol and an increase in triglyceride (TG), and LDL cholesterol. This worsens the CHD risk (Wark, 2004). It has been documented that a 20% reduction in the level of HDL results in 20% increase in CVD rates (Gordon DJ, 1989). However, despite this recognised association between gender and lipid levels, male gender is accepted as an independent risk factor for the development of CVD. There is a paucity of data addressing CV risk specific to gender. However, gender is a component of all CV risk assessment tools with male gender adding a weighting to the CV risk calculation (Wilson, 1998, society, 2005).

Several studies have demonstrated that Indians residing in India have a high prevalence of traditional CV risk factors (Misra et al., 2004). In addition, Asian Indian migrants and their offspring also appear to have increased CV risk compared to the native populations of their host countries (Misra and Khurana, 2011, Anand SS, 2000, Enas et al., 1997, Venkataraman R, 2004, S.S. Liem, 2009). For any given conventional CV risk factor the CHD risk in Indians is higher than Europeans, double that of Americans and seven times higher than other Asians (Enas, 2000). Among Indians, the CV risk is higher in urban than rural populations; possibly because urbanisation is associated with reduced physical activity and increased consumption of fat and calorie rich food, which causes abdominal obesity, insulin resistance and dyslipidaemia.

In India, obesity is more associated with affluent socioeconomic status (perhaps reflecting reduced exercise and high calorie intake), whilst poverty is more frequently associated with low body weight and malnutrition (Gaiha et al., 2011). This is in marked contrast to western countries, where obesity is linked to poverty. In western countries lower socioeconomic groups seem to have less understanding of healthy dietary intake and poverty related factors may contribute to limited food choices. These appear to result in increased intake of more calorie dense food in their diet (Edwards and Clarke, 2009).

South Asian Indians have an increased prevalence of type 2 diabetes, which could be due to the effect of the thrifty gene hypothesis, which suggests an interaction between genetic predisposition and environment (R Ramaraj, 2008). The 'thrifty genes' enable an individual to efficiently collect and process food to deposit fat during periods of abundance (Neel, 1962).

In India, there are additional, geographical variations in CV risk. For example, South Indians have been reported to have an increased prevalence of CV risk factors compared to North Indians (Begom R, 1995). The WHO project on sentinel surveillance of Indian industrial populations has demonstrated that in India the highest prevalence of obesity and a high waist circumference is observed in Hyderabad, Andhra Pradesh. (Reddy et al., 2002)

However, there are minimal data describing traditional CV risk factors in South Asian Indians with RA. If CV risk factors are highly prevalent in the Indian population, it is possible that development of RA in this population will not be associated with additional elevation of this risk. This work was undertaken to describe the prevalence of traditional CV risk factors in a cohort of South Asian Indian RA patients residing in Hyderabad.

5.2 Aims

The primary aim of this study is to report the prevalence of traditional CV risk factors in Asian Indian patients with RA.

The secondary aim was to explore the prevalence of traditional CV risk factors in RA cases stratified by gender and rheumatoid factor status.

5.3 Patients and methods

5.3.1 Patients

The RA cohort was recruited from a tertiary care rheumatology centre in Hyderabad, South India. The details of the rheumatology centre and its patient population is described in chapter 4 section 4.8. Consecutive eligible patients with a diagnosis of RA, attending the Sri Deepti Rheumatology centre were invited to participate. The eligibility criteria for the study are described in detail in chapter 4 table 4.1.

The study was approved by the institutional ethics committee of Sri Deepti Rheumatology Centre and all subjects gave written informed consent to participate.

5.3.2 Data collection

To maintain uniformity, a standard pro forma, was used to collect information from the study participants. Demographic details including age and gender were recorded. The details of selection of the cohort and assessments are described in detail in chapter 4 section 4.12.

5.3.3 RA disease characteristics

Rheumatoid arthritis related details including disease duration, rheumatoid factor status, and detailed history of current medications including NSAIDS, steroids, DMARDs and biological response modifiers were taken in the RA cohort. The patients were examined for 28 tender and swollen joints. Patient global assessment of disease activity using the visual analogue scale (VAS) was recorded and the disease activity score (DAS) was calculated with the DAS 28 calculator (Alfons and Michiel online DAS calculator). In total, seven RA disease markers studied were RF, disease duration, tender joint count, swollen joint count, ESR, CRP, global VAS and DAS was calculated. (http://www.das-score.nl/dasculators.xls).

5.3.4 CV risk assessments

Participants underwent a detailed analysis including measurements of height, waist and hip. Patients were weighed, clothed with footwear removed (Krups Mfg in India) and weight was recorded in kilograms (Kgs). Height was measured using a fixed stadiometer and was recorded in metres. Body mass index was calculated. Waist and hip

circumferences were measured using a hand held tape measure as described in chapter 4 section 4.10 . A high waist hip ratio was defined as more than 0.95 in females and more than 1.00 in males according to NCEP ATP (III, 2002). Blood pressure was measured after sitting at rest for 15 minutes (Diamond regular (IS3390) Mfg in India) see chapter 4 section 4.9. The mean of 3 readings was calculated and entered on the paper CRF.

Traditional CV risk factors recorded included modifiable and non modifiable risk factors. In total eight risk factors including lipid profile were studied. Participants were asked about family history of HTN, Diabetes and CVD. A family history of CVD was defined as a first degree relative with atherosclerotic CVD, that developed, before the age of 55 years in males, and before 65 years in females (NCEP, 2001)

A detailed past medical history was recorded for each patient. A coexisting disease not related to RA was defined as a co morbid condition. History of co morbid hypertension, diabetes mellitus, hypothyroidism, and CVD were taken. Co morbidity was considered if the subject had a diagnosis of another condition or was on medication for a particular problem.

History of smoking was taken and the subjects were classified as smokers and non-smokers. Ex smokers for more than a year were considered as non smokers. History of a vegetarian diet was recorded.

Laboratory evaluation included non-fasting lipid profile, ESR, RF, CRP, and fasting blood glucose. A chest X- ray was taken in subjects who had not had such imaging within the prior three months.

Coronary risk assessment was done and metabolic syndrome criteria were applied as described in chapter 4 section 4.15 and 4.16

5.3.5 Analysis

The data was analysed by simple descriptive statistics. Categorical variables were described by number (n) and percentage (%). Continuous data was described as median and inter quartile range [IQR] for non parametric data. Risk factors such as HTN, DM, BMI, W:H ratio were presented as both continuous variables and categorical variables. The categorical variables were defined according to cut offs for elevated values as suggested by the British Hypertension society and high cut off of NCEP ATP III respectively (JAMA 2001). The composite 10 year risk score of a CHD event calculated by Framingham and JBS were treated as continuous variables and categorical variables were generated based on elevated and high CHD risk levels (see table 4.7 chapter 4)

Chi squared test was used to compare the prevalence of categorical variables and Wilcoxon's Ranksum test was used for comparing non parametrically distributed continuous data. The RA disease variables in the cohort were stratified by gender and RF status and were analysed.

5.4 Results

5.4.1 RA disease variables

The RA disease related characteristics in the cohort of 800 RA patients are shown in table 5.1. Patients had median disease duration of 4 years. The majority of the cohort was RF positive 629 (78.6%). High ESR and CRP were found in most of the participants with the median being 63 [IQR 42, 84] for ESR and 48 [IQR 24, 84] for CRP. Patients had a high disease activity - the Median DAS 28 in the RA cohort was 5.7 [4.5, 6.9]. High disease activity (DAS 28 > 5.2) was observed in 59.8% of individuals (n = 478).

Table 5.1 RA disease characteristics

Baseline Parameters	**Description**	**Patients n = 800**	
RF positive	n (%)	629	(78.6)
Duration of disease (yrs)	med [IQR]	4	[1.6,10]
CRP (mg/dl)	med [IQR]	48	[24,48]
ESR	med [IQR]	63	[42,84]
TJC	med [IQR]	9	[4,17]
SJC	med [IQR]	4	[2,8]
VAS	med [IQR]	60	[50,90]

RF - rheumatoid factor, DAS - disease activity score based on 28 joint counts, ESR - erythrocyte sedimentation rate, TJC - tender joint count, SJC - swollen joint count, global health VAS - visual analogue scale, and IQR – inter quartile range.

The medication used by patients for their RA treatment is presented in table 5.2. All the patients using steroids were on a dose of 7.5 mg or less prednisolone per day.

Steroids were used by 41.8% and NSAIDs by 68.9% RA patients. A combination of NSAIDS and steroids was used by 37.8 % of patients. Methotrexate was used by most of the participants (91.6%). Other biologic or non biologic DMARDS were used in

combination with methotrexate. The most frequently used combination DMARDs were methotrexate and hydroxychloroquine (n= 145); methotrexate and leflunomide (n=130); methotrexate and sulphasalazine (n=56) and methotrexate and etanercept (n=33). 8.4% of individuals who were not on methotrexate either had a mild disease, were intolerant of methotrexate, or were planning progeny (n=16).

Table 5.2 Medicines used by RA patients

Medications used	n = 800	percentage
NSAIDS	551	68.9
Steroids	334	41.8
Methotrexate	733	91.6
Leflunomide	130	16.3
Hydroxychloroquine	148	18.5
Sulfasalazine	59	7.4
Etanercept	33	4.1
Steroids + NSAIDS	302	37.8

NSAIDS – non steroidal anti inflammatory drugs

5.4.2 General descriptive data in RA cohort

The RA cohort comprised 800 consecutive adult patients fulfilling 4 out of 7 of the 1987 ACR classification criteria (Arnett et al., 1988). The mean age of the RA patients was 46.4 years, 668 were females (83.5%), and 142 were males (26.5%) see Table 5.3. The female : male ratio was 5:1. None of the females and only twelve males reported smoking histories. This cohort had a high family history of HTN (n=236 (29.5%)), DM (n=252 (31.5%)) and CVD (n=101 (12.6%)).

Table 5.3 Descriptive baseline data in the cohort

	Cases n = 800		
Parameters	**description**		
Age in yrs	med [IQR]	46.5	[38, 55]
Female	n (%)	668	(83.5)
Male	n (%)	132	(16.5)
Vegetarian	n (%)	213	(26.6)
Smoking	n (%)	12	(1.5)
Family History CVD	n (%)	101	(12.6)
Family History DM	n (%)	252	(31.5)
Family History HTN	n (%)	236	(29.5)
Co morbid DM	n (%)	138	(17.3)
Co morbid HTN	n (%)	236	(29.5)
Co morbid CVD	n (%)	5	(0.6)
Hypothyroid	n (%)	82	(10.5)
Waist : Hip ratio	med [IQR]	0.92	[0.86,0.98]
High Waist : Hip ratio *		218	(27.5)
BMI Kg/m2	med [IQR]	26.1	[23.1,29.7]
High BMI (BMI >25)	n (%)	481	(60.1)
Systolic mmHg med	med [IQR]	130	[120, 140]
Diastolic mmHg med	med [IQR]	80	[80, 90]

CVD- Cardiovascular Disease, HTN- Hypertension, DM- Diabetes Mellitus, BMI- Body Mass Index, IQR- Inter Quartile Range *Waist:Hip ratio classified as high if ≥ 0.95 in Women & if, ≥1 in Men)

The RA cohort had a high prevalence of CV related co morbidities especially with 29.5% reporting HTN and 17.3% having a diagnosis of type 2 DM. Anecdotal evidence of co morbid CV was recorded in five patients and they were not on any treatment of the same. The presence of these co morbidities was important as they are part of the CV risk assessment. Multiple co morbidities were reported in 100 (12.5%) of the cohort. Hypothyroidism was reported by 82 participants. Hypertension, Diabetes and Hypothyroidism were present together in 10 RA patients.

High waist hip ratios were observed in 27.5% of the participants. The median BMI was 26.1 Kg/m^2 and 481 (60%) were classified as being overweight or obese as per the WHO classification (WHO 2000).

5.4.3 Fasting blood glucose and lipid parameters in RA cohort

The median fasting blood glucose in the RA cohort was 87 mg/dl Table 5.4. When the patients were categorized as having fasting blood glucose of more than 100 mg /dl (NCEP, 2001) it was found that 27.5 % of participants had high blood glucose. Using a cut off of 126mg/dl, the level taken for diagnosis of diabetes mellitus (DM) according to NCEP ATPIII (NCEP, 2001) it was noted that 7.1% had fasting blood glucose in the diabetic range. Whilst most of these patients were known to have DM, 20% were not known to have a diagnosis of co morbid DM. These patients were informed of this abnormality and were encouraged to adopt dietary change, lose weight and increase exercise levels. Repeat blood glucose measurements were organised for these patients to allow diagnosis of DM to be made.

Table 5.4 Fasting blood glucose in cases

Parameters	**Description**	**RA cases n=800**	
FBS	med [IQR]	87	[76,102]
Fasting blood glucose >100mg/dl	n (%)	220	27.5
FBS in DM range >126 mg/dl	n (%)	57	7.1

FBS- Fasting Blood Sugar, DM- Diabetes mellitus

The median lipid profile was within the normal range see Table 5.5. A quarter of the patients (25.4%) had T-Chol more than 200 mg/dl. High TG >150 mg/dl was seen in 39.9% of cases, 5.9% had low HDL-Chol <40mg/dl and 13.3% had a T-Chol: HDL-Chol ratio more than 4.5.

Table 5.5 Baseline lipid parameters and elevated parameters in cohort

Baseline Values	Description	Patients n = 800	
T- Chol	med [IQR]	175	[154, 201]
T-Chol >200mg/dl	n (%)	203	25.4
HDL- Chol	med [IQR]	48	[45, 51]
HDL- Chol <40mg/dl	n (%)	47	5.9
LDL- Chol	med [IQR]	99	[79.5, 120.5]
TG	med [IQR]	132.5	[98, 184]
TG >150mg/dl	n (%)	319	39.9
T-Chol : HDL-Chol ratio	med [IQR]	3.7	[3.3, 4.2]
T-Chol :HDL- Chol ratio >4.5	n (%)	106	13.3

T-Chol – Total Cholesterol, HDL-Chol- High Density Lipoprotein Cholesterol, LDL-Chol- Low Density Lipoprotein Cholesterol, TG – Triglycerides

5.4.4 Framingham and JBS calculated CVD risk scores in the RA cohort

Table 5.6 shows the composite 10 year risk of CVD calculated using JBS and Framingham risk score calculator. The median Framingham risk score was 4.0% risk of a CHD event in a 10 year period. However, over a quarter of the cohort (212 (26.5%) patients) had an elevated CHD risk score (defined as >=10%) and 11% had high CHD risk with Framingham risk scores above 15%.

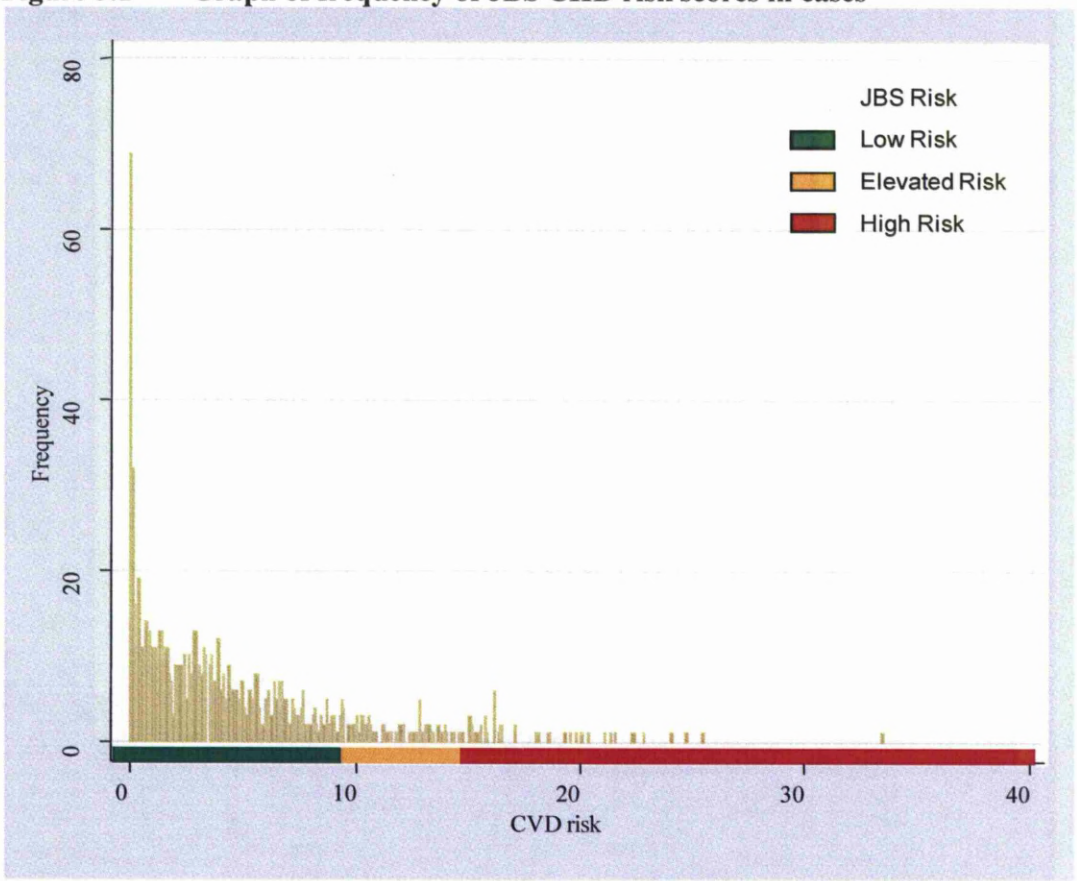
The CHD risk scores were lower when calculated using JBS. The median risk score of a CHD event according to JBS was 3.2% based on systolic blood pressure and 3.6%

when based on diastolic BP. A much smaller proportion of the cohort was identified as having elevated CHD risk (12.6%) or high CHD risk (5.6%) when CHD risk was assessed using JBS. When the JBS scores were divided into tertiles it is clear that the data is skewed to the left with most patients having very modest CHD risk scores. The range of JBS CHD risk scores for patients is shown in figure 5.1.

Table 5.6 Calculated CHD risk scores in the cohort

		Patients n = 800	
	Calculated CHD risk		
Based on Framingham	10 yr CHD risk % med [IQR]	4	1, 8
	10 year CHD risk >10% n (%)	212	26.5
	10 year CHD risk >15% n (%)	90	11.3
*Based on JBS	10 yr CHD risk % med [IQR] (systolic)	3.2	[0.9,6.6]
	10 yr CHD risk % med [IQR] (diastolic)	3.6	[0.9, 7.3]
	10 year CHD risk >10% n (%)(systolic)	101	(12.6)
	10 year CHD risk >15% n (%)(systolic)	45	(5.6)
	Tertiles of 10 year CHD % risk (Systolic BP)		
*Based on JBS	<1.5%	257	(32.1)
	1.5- <5%	266	(33.3)
	>5%	277	(34.6)

Figure 5.1 Graph of frequency of JBS CHD risk scores in cases



5.4.5 Metabolic syndrome in RA cohort

Criteria for metabolic syndrome were applied to all RA patients see Table 5.6. Nearly half of the cohort (46% of RA patients) had three out of five criteria and qualified as having metabolic syndrome see Table 5.7. Only 7.4% of the cohort did not have any of the criteria for calculating metabolic syndrome according to the ATPIII classification (NCEP, 2001).

Table 5.7 Meets criteria for ATPIII metabolic syndrome in cases

		Patients n = 800	
		n	%
ATP III score	0	59	7.4
	1	156	19.5
	2	217	27.1
	3	235	29.4
	4	119	14.9
	5	14	1.8
ATPIII	Meets Criteria for MS	368	46.0

5.5 Descriptive data in the RA cohort stratified by gender

5.5.1 RA disease variables stratified by gender

Females in the RA cohort had a trend for longer disease duration and were more frequently positive for RF. The swollen joint count, tender joint count, global VAS was numerically higher in females. The disease activity parameters like ESR and CRP were similar. No difference was observed in the DAS 28 in male and female RA patients see Table 5.8.

Table 5.8 RA disease variables stratified by gender

Baseline Parameters	Females n = 668		Males n = 132		P value
RF positive n (%)	528	79.1	101	76.5	NS
Duration of disease(years)	4	[2,10]	3	[1,8]	NS
DAS 28 Mean (SD)	5.7	(1.6)	5.6	(1.6)	NS
C reactive protein(mg/dl)	42.0	(21.8)	41.8	(21.9)	NS
ESR Med [IQR]	63	[43,84]	64	[40,84]	NS
TJC Mean (SD)	11.3	(8)	10.7	(7.7)	NS
SJC Mean (SD)	5.9	(5.4)	5.6	(4.9)	NS
VAS Mean (SD)	65.2	27.7	64.3	(29.0)	NS

RF-Rheumatoid Factor, DAS- Disease activity score, ESR- Erythrocyte Sedimentation Rate, TJC- Tender Joint Count, SJC- Swollen Joint Count, Global Health VAS- Visual Analogue Scale, and SD- Standard Deviation.

5.5.2 General descriptive data

The eight hundred patients in RA cohort were stratified by gender and analyzed. The females in the cohort were 668 and 132 were males. Females in the cohort were younger and were more often vegetarian this difference was not statistically significant. There were very few smokers in the cohort (n=12 (9.09%)). None of the females smoked. Family history of CVD was similar in the two groups (12.1%). Co morbidities such as DM and HTN were more frequently seen in males (15.7% vs 25.0% and 28.6% vs 34.1%) this difference did not display a statistical difference. Hypothyroidism was common in females (11.1% vs 3.03%). This difference was statistically significant ($p<0.01$). The difference in median waist: hip ratio was significant ($p<0.01$). Though high waist : hip ratio of more than 0.95 was more frequently observed in females 27.8% it was not statistically significant. Females also exhibited a high BMI in the overweight / obese range (>25) 63.1% vs 45.5% which was statistically significant ($p<0.001$). The

median systolic and diastolic pressure was similar in the groups but when a cut off of >140 mm of Hg systolic and > 90 mm diastolic BP was used there was a difference between male and female RA cohort ($p<0.03$, <0.01) see Table 5.9.

Table 5.9 Descriptive data in RA cohort stratified by gender

Parameter	Females n=668 (83.5%)		Males n=132 (16.5%)		p value
Demographics					
Age in yrs, med [IQR]	46	[38, 54.5]	49	[40,56]	NS
Vegetarian n (%)	185	(27.7)	28	(21.2)	NS
History of CVD risk factors					
Smoking n (%)	00	(00)	12	(9.09)	-
F history CVD n (%)	81	(12.1)	16	(12.1)	NS
Co morbid DM n (%)	105	(15.7)	33	(25.0)	NS
Co morbid HTN n (%)	191	(28.6)	45	(34.1)	NS
Co morbid CVD n (%)	4	(0.6)	1	(0.76)	NS
Hypothyroid	78	(11.7)	4	(3.03)	p<0.01
Anthropometric measurements					
waist : hip med[IQR]	0.91	[0.86, 0.98]	0.97	[0.91, 0.99]	p<0.001
High W:H ratio n (%)	186	(27.8)	32	(24.2)	NS
BMI med [IQR]	26.4	[23.4,30.0]	24.7	[22.2,27.4]	p<0.001
BMI> 25 kg/m2 n (%)	421	(63.1)	60	(45.5)	p<0.001
BP mm Hg					
Systolic med[IQR]	130	[120,140]	130	[120,140]	NS
High Systolic >140	173	25.9	46	34.9	p=0.03
Diastolic med[IQR]	80	[80,90]	80	[80,86]	NS
High Diastolic >90	251	37.6	64	48.5	p=0.01

CVD- Cardiovascular Disease, HTN- Hypertension, DM- Diabetes Mellitus, BMI- Body Mass Index, IQR- Inter Quartile Range, F history- Family history, W:H ratio- Waist: Hip ratio
*Waist:Hip ratio classified as high if ≥ 0.95 in Women & if, ≥1 in Men)

5.5.3 Fasting blood glucose and lipid parameters in RA cohort stratified by gender

Though the fasting blood glucose was higher in males who also exhibited a trend for lower lipid parameters. The high FBS and low HDL-Chol was significant statistically ($p<0.05$) see Table 5.10

Table 5.10 Fasting blood glucose and lipid parameters in RA stratified by gender

Parameter	Females n = 668 (83.5%)		Males n = 132 (16.5%)		p value
F B S med [IQR]	86	[76,101]	92	[77.5,104.5]	NS
High FBS	174	26.1	46	34.8	p<0.05
FBS in DM range	43	6.4	14	10.6	NS
T- Chol med [IQR]	175.5	[155,202]	171	[150,195.5]	NS
High T-Cho	174	26	29	22.0	NS
HDl- Chol med [IQR]	48	[45,51]	47	[44,50]	NS
Low HDL-Chol	34	5.1	13	9.9	p<0.05
LDL-Chol med [IQR]	99	[43,50]	97	[80.5,121]	NS
High LDL-Chol	31	4.6	9	6.8	NS
TG med [IQR]	133	[98,185]	132	[95,179]	NS
High TG	272	40.7	47	35.6	NS
T -Chol: HDL-Chol	3.7	[3.3,4.2]	3.6	[3.3,4.2]	NS
High T-Chol:HDL ratio	6	0.9	2	1.5	NS

5.5.4 Framingham and JBS calculated CHD risk scores in the RA cohort stratified as per gender

The composite 10 year risk score of CHD event was calculated as per Framingham and JBS calculator see Table 5.11. The median risk score was higher in males (7% vs 4%). Males exhibited a higher elevated score (>10%) which was almost twice that of females. When the group was further categorized as having a high score (>15%) males had a four times higher risk score when compared to females (30.3% vs 7.5%). There

was a statistical significance in the gender stratified RA cohort in median, elevated and high categories of the Framingham CHD risk scores see Table 5.11

Table 5.11 Calculated CHD risk scores in the RA cohort

	Parameters	Females n= 668 (83.5%)		Males n=132 (16.5%)		p value
Based on Framingham	10 yr CHD risk % med [IQR]	4	[0, 8]	7	3, 12	p<0.001
	10 year CHD risk >10% n (%)	155	23.2	57	43.2	p<0.05
	10 year CHD risk >15% n (%)	50	7.5	40	30.3	p<0.001
*Based on JBS	10 yr % CHD risk med [IQR] (systolic)	2.8	[0.7,5.95]	5.7	[3.2,10.3]	p<0.001
	10 yr % CHD risk med [IQR] (diastolic)	3	[0.6, 6.6]	6.3	[3.3, 11.8]	p<0.001
	10 year CHD risk >10% n (%) (systolic)	65	(9.7)	36	(27.3)	p<0.001
	10 year CHD risk >15% n (%) (systolic)	24	(3.6)	21	(16.0)	p<0.001
Tertiles of 10 year CHD % risk (Systolic BP))						
*Based on JBS	<1.5%	240	(35.9)	17	(12.9)	p<0.001
	1.5- <5%	226	(33.8)	40	(30.3)	p<0.001
	>5%	202	(30.2)	75	(56.8)	p<0.001

The median systolic and diastolic risk score of a CHD event according to JBS was higher in males. A higher elevated (>10%) risk was found in males (27.3% vs 9.7%). High score of >15% was found to be more than four times higher in males. Males more frequently had a high score in the highest tertile (>5%) tertile of CHD risk and females more frequently had a CHD risk score in the <1.5, 1.5- <5 range. The CHD risk score in median, elevated, high and all the tertiles was statistically significant see Table 5.11.

5.5.6 Metabolic syndrome in RA cohort stratified by gender

The gender stratified ATPIII metabolic syndrome criteria in the RA cohort revealed a significant difference between male and female RA cohort. More than half of the female RA population (50.9%) meet the criteria for metabolic syndrome. There was a

statistical difference in the females (5.9%) and males (14.4 %) who did not have any criteria of metabolic syndrome see Table 5.12.

Table 5.12 Meets criteria for ATPIII metabolic syndrome

		Patients n = 800				p value
		Females		Males		
		n	%	n	%	
ATP III score	0	40	5.9	19	14.4	p<0.05
	1	108	16.2	48	26.4	p<0.05
	2	180	27.0	37	28.0	NS
	3	214	32.0	21	15.9	p<0.001
	4	112	16.8	7	5.3	p<0.001
	5	14	2.1	0	0	-
ATPIII	Meets Criteria for M S	340	50.9	28	21.2	p<0.001

5.6 Descriptive data in the RA cohort stratified by gender stratified by RF status

5.6.1 RA disease variables stratified by RF status

The RA cohort was stratified as per rheumatoid factor status. RF was found to be positive in 629 cases and 171 were negative for RF see Table 5.13. The RF positive group was older (47 vs 45 yrs) and were more often females (n= 528 (83.9 %)). The RF positive group had longer disease duration (5 yrs vs 3 yrs) see Table 5.13. A trend for numerically higher tender, swollen joints and global VAS and ESR was observed in the RF positive group but this was not statistically significant.

Table 5.13 RA disease variables as per RF

Parameters	Description		RF + n = 629		RF- n = 171		p value
RA details							
Disease duration	years	med[IQR]	5	[2, 10]	3	[1, 6]	p<0.001
TJC		mean(SD)	11.4	8.0	10.4	7.7	NS
SJC		mean(SD)	5.9	5.3	5.6	5.2	NS
VAS	mm	mean(SD)	65.4	27.7	63.5	28.3	NS
DAS 28			5.7	1.6	5.6	1.7	NS
ESR	mm/hr	med [IQR]	65	[43, 85]	57	[40, 80]	p<0.05
CRP	mg/dl	mean(SD)	42.8	21.9	39.0	30.0	p<0.001

The RF positive group displayed a trend for increased use of NSAIDs (70.0% vs 64.9%) and steroids (43.3% vs 41.3%) see Table 5.14. Methotrexate use was significantly higher in the RF positive group (93.3% vs 85.4%). There was a 2 fold increase in use of leflunomide by RF positive patients when compared to the RF negative group. Etanercept was more frequently used in the RF positive group (4.8% vs 1.8%). Sulphasalazine (9.4% vs 6.4%) and hydroxychloroquine (23.4% vs 17.2%) were more frequently used in the RF negative group.

Table 5.14 Medicines used by the RA cohort stratified as per RF

Parameters	Description		RF + n = 629		RF - n = 171		p value
NSAIDS n	Yes	(%)	440	(70.0)	111	(64.9)	NS
Steroids n	Yes	(%)	260	(41.3)	74	(43.3)	NS
Methotrexate	Yes	(%)	587	(93.3)	146	(85.4)	p<0.001
Leflunomide	Yes	(%)	114	(18.1)	16	(9.4)	NS
Etanercept	Yes	(%)	30	(4.8)	3	(1.8)	NS
Sulphasalazine	Yes	(%)	43	(6.4)	16	(9.4)	NS
HCQ	Yes	(%)	108	(17.2)	40	(23.4)	NS

5.6.2 General descriptive data in the RA cohort stratified as per RF status

RF positive patients were more frequently vegetarian see Table 5.15. Though the number of smokers in the cohort was very few it was found that smoking was very strongly associated with RF positive status ($p<0.05$). Interestingly family history of CVD was more frequent in the RF negative group. The RF positive group displayed increased prevalence of co morbid conditions such as DM (8.4% vs 2.9%), HTN (31.2%, 23.4%) and hypothyroidism (10.1% vs 8.2%). High blood pressure of >140 and >90 mm of Hg was similar in the two groups but RF negative patients demonstrated a trend for higher diastolic BP.

The median BMI was slightly higher in RF negative group who also frequently exhibited BMI of > 25 which is in the overweight / obese range (67.3% vs 58.2%). The categorical BMI of < 25 was more often seen in RF positive group (41.2% vs 32.2%) where as the RF negative group had an increased prevalence of high BMI 25-< 30 (42.7% vs 36.7%) and > 35 BMI (24.6% vs 21.6%) respectively. Waist: hip ratio was similar in the two groups. High waist hip ratio of >0.8 in females and >1 in males was seen in 28.6% of RF positive and 22.2% in the RF negative group.

Table 5.15 Descriptive data in RA cohort stratified by RF status

Parameters	Description		RF + n = 62978.6%)		RF- n = 171 (21.4%)		p value
Demographics							
Age	Years	Med [IQR]	47	[38, 55]	45	[37, 55]	NS
Female	n	(%)	528	(83.9)	140	(81.9)	NS
Vegetarian	n	(%)	177	(28.1)	36	(21.1)	NS
CV risk factors							
Smoking	n	(%)	11	(1.75)	1	(0.58)	p<0.05
F history CVD	n	(%)	70	(11.3)	27	(15.8)	NS
DM	n	(%)	116	(18.4)	22	(12.9)	NS
HTN	n	(%)	196	(31.2)	40	(23.4)	NS
CVD	n	(%)	3	(0.5)	2	(1.2)	NS
Hypothyroid	n	(%)	68	(10.1)	14	(8.2)	NS
Blood pressure							
BP Systolic	mmHg	Med[IQR]	130	[120, 140]	130	[120, 140]	NS
BP Diastolic	mmHg	Med[IQR]	80	[80, 90]	80	[80, 90]	NS
High BP Systolic	>140 n		172	27.3	47	27.5	NS
Diastolic	> 90 n		252	40.1	63	36.8	NS
Measurements							
BMI	Kg/m^2	Med[IQR]	25.9	[22.8, 29.6]	26.6	[24.1,30.0]	NS
High BMI	>25	(%)	336	(58.2)	115	(67.3)	NS
Cat BMI	<25	(%)	262	(41.2)	56	(32.2)	NS
	25 -< 30	(%)	231	(36.7)	73	(42.7)	NS
	>35	(%)	136	(21.60)	42	(24.6)	NS
W : H ratio		Med [IQR]	0.92	[0.86, 0.98]	0.91	[0.86, 0.96]	NS
High W:H	>0.95 F > 1 M	(%)	180	(28.6)	38	(22.2)	NS

5.6.3 Fasting blood glucose and lipid parameters in RA stratified by RF status

Median fasting blood glucose and fasting blood glucose of more than 126 mg/ dl which is in the diabetic range was similar in the RF positive and RF negative group.

Total cholesterol was found to be significantly higher in the RF negative group who also exhibited an increased number of patients having a high T-Chol > 200 mg/dl see Table 5.16. Low HDL cholesterol (7.6% vs 5.4%) and significantly high triglyceride (48.0% vs 37.7%) (P<0.05) were more frequently observed in the RF negative group. There was trend for higher LDL cholesterol in the RF negative group. The T-Chol: HDL-Chol was similar in the two groups.

Table 5.16 Fasting blood glucose and lipid parameters stratified by RF status

Parameters	Description		RF + n = 629		RF- n = 171		p value
FBS	mg/dl	Med [IQR]	86	[77, 102]	87	[76, 102]	NS
High FBS>126	mg/dl	n (%)	173	(27.5)	47	(27.5)	NS
T-Chol	mg/dl	med [IQR]	173	[153, 198]	182	[158, 210]	p<0.05
High T-Chol	> 200	n (%)	145	(23.1)	58	(33.9)	p<0.05
HDL -Chol	mg/dl	med [IQR]	48	[45, 51]	49	[45, 52]	NS
Low HDL-Chol	< 40	n (%)	34	(5.4)	13	(7.6)	NS
LDL-Chol	mg/dl	med [IQR]	97	[79, 119]	102	[82, 127]	NS
High LDL C		n (%)	31	4.9	9	5.2	NS
T-Chol: HDL		med [IQR]	3.7	[3.3, 4.1]	3.8	[3.3, 4.3]	p=0.002
High TChol:HDL		n (%)	5	0.79	3	1.75	NS
TG	mg/dl	med [IQR]	130	[97, 178]	147	[102, 207]	p=0.007
High TG	>150	n (%)	237	(37.7)	82	(48.0)	p<0.05

5.6.4 Framingham and JBS calculated CHD risk scores in the RA cohort stratified as per RF status

The composite 10 year CVD risk score for the probability of a CV event was calculated as per Framingham and JBS calculator see Table 5.17. Though there was no statistically significant difference in the CHD risk scores the JBS calculation revealed that the median score was higher in the RF positive group who also exhibited a trend for having elevated (>10%) (13.2% vs 10.5%) and high (>15%) (5.6% vs 4.7%) score of JBS. The number of patients in tertiles of CV risk as per JBS (<1.5, 1.5- <5% and >5%) was more in RF positive group where as the RF negative group had more patients in the <1.5% (32.6%).

Table 5.17 Calculated CHD risk scores in the RA cohort stratified as per RF status

Parameters	Description		RF + n = 629		RF- n = 171		p value
CV risk	Systolic	med [IQR]	3.4	[1, 6.7]	2.8	[0.7, 6]	NS
CV risk	Diastolic	med [IQR]	3.7	[1, 7.5]	3	[0.7, 6.5]	NS
Tert CVD	<1.5	n(%)	195	(31.0)	62	(36.3)	NS
	1.5- <5	n(%)	210	(33.4)	56	(32.6)	NS
	>5	n(%)	224	(35.6)	53	(30.1)	NS
JBS CHD >10%		n(%)	83	(13.2)	18	(10.5)	NS
JBS CHD>15%		n(%)	37	(5.6)	08	(4.7)	NS
Fram CHD risk score		med [IQR]	4	[1, 10]	4	[0, 8]	
Fram CHD >10%		n(%)	172	27.3	40	23.4	NS
Fram CHD >15%		n(%)	75	11.9	15	8.8	NS
M S		n(%)	286	45.5	82	48.0	NS

5.7 Discussion

This cohort of young South Asian Indian RA patients has demonstrated a very high prevalence of traditional CV risk factors despite their age, predominantly female population and negligible smoking history. The most common co morbidity observed was hypertension, followed by DM (30%, 17%). It was interesting to note that nearly half the patients met criteria for metabolic syndrome, which may reflect clustering of multiple CVD risk factors in these RA patients. A quarter of the individuals had an elevated (>10%) CHD risk score, when this was calculated using Framingham CHD risk score. A much smaller proportion was identified as having elevated CHD risk when the JBS risk calculator was used.

Gender stratified analysis revealed that male gender has a strong association with CV risk factors like hypertension, diabetes and smoking. This is in accordance with published literature. The QUEST RA study demonstrated increased prevalence of CV risk factors in males who also had increased CV events. The authors confirmed the association of traditional CV risk factors to CV morbidity (Naranjo et al., 2008). However, this study did not calculate the CHD risk score. The males in our cohort had significantly higher prevalence of elevated (>10%) CHD risk which was double that of females. This difference was more marked when high CHD risk (>=15%) was compared by gender in the RA cohort. Males had a 4 fold increased prevalence of high CHD risk when compared to females. Whilst this may be explained by the increased weighting in the risk calculation given to men it is interesting that the difference is more marked at the high CHD risk cut off. Very few previous studies have looked at the risk

score specific to gender. The high CHD risk in males is an important finding as our cohort was younger than the study population of most of the published data and another important feature is that there are negligible smokers in the population.

More than half of the females in this cohort had met the criteria for metabolic syndrome. Whilst the published data reports a high prevalence of metabolic syndrome in the South Asian Indian population this seems a remarkably high prevalence in the RA cohort. The reasons for this high prevalence are not clear but may reflect the relatively affluent socioeconomic background of this patient population or possibly the urban setting of this study. We have already acknowledged that obesity is associated with both these factors and it may be that high prevalence of obesity in the patients studied is responsible for this high metabolic syndrome prevalence. There is a need to compare the prevalence of metabolic syndrome in a similar non RA control group to explore whether this risk factor is associated with RA. This is in accordance with published data that metabolic syndrome is high in the South Asian Indian population (Misra and Vikram, 2004). However, it is remarkable that this RA patient group had such a high prevalence of metabolic synd.

No difference was found in the RA disease activity between males and females.

Increased co morbidities and a trend for higher 10 year probability of CHD event was observed in the RF positive patients. Though the cohort had very few smokers it was found that all but one of the twelve smokers belonged to the RF positive group. This

might reflect the association between smoking and the development of RF in RA (Criswell et al., 2002). However the number of smokers was very small in this cohort. It is unlikely that the increased 10 year CHD risk is due to the effect of smoking alone. The occurrence of association between CVD mortality and RF positive status has been explored (Goodson et al., 2008). These authors have suggested that RF positive status is associated with more severe disease and higher inflammatory disease burden contributes to the excess CVD mortality observed through inflammation accelerating atherosclerosis.

Higher waist hip ratio was found in the RF positive group. The RF positive cohort had a trend for low BMI of <25 as the disease activity was high the possibility of rheumatoid cachexia cannot be ruled out. Therefore it seems that RF positive patients have more of a centripetal distribution of body fat. This suggests that these patients may have more rheumatoid cachexia and more abdominal fat. We were not able to measure percentage body fat or distribution of body fat in this study. It would be interesting to measure this in future studies. Rheumatoid cachexia is associated with inflammation and abdominal body fat distribution is associated with increased CHD risk and metabolic syndrome.

The RF positive group displayed increased CHD risk scores when compared to RF negative group. Though RA disease activity was similar in the two groups, the RF positive group displayed increased use of NSAIDS, steroids, methotrexate, leflunomide and etanercept whereas sulphasalazine and hydroxychloroquine were frequently used by the RF negative group. Rather surprisingly the RF negative patients had a high family

history of CVD, a trend for higher diastolic BP, higher BMI and higher T-Chol, TG and low HDL-Chol. This interesting finding needs to be studied further.

The strengths of this study are the large number of patients studied. To my knowledge this is the largest cohort of Indian RA patients in whom traditional CV risk factors were studied and their composite CV risk calculated. The large number increases the statistical power of the study, affords better potential for the results to be generalised to the wider Indian RA population, allows research questions to be better tested and more reliability for the means obtained. The fact that Hyderabad is a cosmopolitan city, catering to individuals from disparate societies and beliefs, further increases the scope for generisability of the results. Controls free from inflammatory arthritis were matched for age, gender, ethnic and social background (See chapter 4 section 4.7). Finally, this study has generated a large database of RA patients and matched controls, which can be helpful in further studies.

Our findings are consistent with earlier published literature. Studies have demonstrated that RA is associated with dyslipidaemia, diabetes mellitus and metabolic syndrome (Han et al., 2006). An increased prevalence of co morbidities in RA has also been observed before (Gabriel et al., 1999a, Wasko, 2004). In a study looking at CV risk factors in rheumatic conditions it was found that increased prevalence of CV risk factors are common in rheumatic diseases (M. Antivalle, 2007, Panoulas et al., 2007) and found hypertension to be highly prevalent in RA and diastolic hypertension was also observed (McEntegart, 2001).

A weakness of this study has been the fact that I was unable to get data from the participants who refused to participate in the study. In addition, as patients in this cohort were recruited from a tertiary care centre, there is a possibility that I recruited more severe cases than would be found in the community. As I enrolled participants from regular outpatient clinic there is also a possibility that patients with well-controlled RA may not have turned up at the clinic, or those patients may not have agreed to participate as they were happy with their disease control and did not want further evaluation. This may potentially explain the high DAS 28 scores of the study participants. Other potentially confounding factors are that our patients were not fully fasted before giving the blood sample. I also was unable to capture the duration of medicines used in the RA group – but, as the median disease duration of the group was 4 years it is unlikely that participants were on medications for long. Most commonly used NSAIDs are celecoxib, etodolac and diclofenac. The type of NSAID used by RA patients was not recorded and this may have affected the results. However, I was not looking at CV events in the study population and it is established that the CV risk factors may be affected by the use of NSAIDs. Goodson et al have demonstrated that NSAID users have displayed reduced CV mortality in an inception cohort of RA patients who were followed for ten years. The mean duration of NSAID use was four years (Goodson et al., 2009). As the median disease duration of RA cohort was 4 years I would not expect the NSAID users to have a longer exposure and perhaps it may not have had an impact on the CV risk factors. When the study was started 1987 ACR criteria were used for classification of RA patients (Arnett et al., 1988)and all participants included in RA cohort fulfilled the criteria. It may have been possible that

few patients with early arthritis and possibly less active disease who could be included using the 2010 criteria (Aletaha, 2010) may have been missed when 1987 criteria were applied. Finally, extra articular manifestations of disease were not recorded.

CV risk prediction early in the disease is important. Our study participants had active disease and disease duration of 4 years and this study suggests the need CV risk estimation early in the disease to address CV risk prevention. The importance of CV risk prediction early in the disease was described by Kremers et al (Kremers et al., 2008) in a study of 553 RA patients and 574 controls. The authors found that 85 % of newly diagnosed RA patients had 1 in 5 chance of developing CV events compared to 40% in controls. In each age group this finding was similar to controls that were 5-10 years older. The authors have suggested prediction of CV risk in RA patients within 10 years of diagnosis as patients suffer from significant pain and stress and CV prevention may be delayed. Another study has emphasized the CV risk prediction early in the disease. The study looking at CV events in early RA followed up for five years have found that occurrence of CV events was explained by traditional CV risk factors and was potentiated by high disease activity (Innala et al., 2011).

The observation that the patients had such a high prevalence of metabolic syndrome of 46% is important, since the general Indian population already has a high prevalence of metabolic syndrome and diabetes (Misra et al., 2010) and inflammation is considered to be a link between obesity, metabolic syndrome and CVD (Gremese and Ferraccioli, 2011).

Very few studies have previously been conducted in Indian RA patients looking at traditional CV risk factors and calculating their CV risk score. Grover et al (Grover et al., 2006) studied 57 Indian RA patients and found that one third of these had subclinical atherosclerosis, which occurred at a relatively young age (41.5 years).
Another case controlled study by Mahajan et al (Mahajan et al., 2008) studied 100 RA patients and 100 controls (mean age 43 years) and found that 33% of RA and 28% of controls exhibited dyslipidaemia and that premature atherosclerosis and carotid plaques were common in the patients with RA.

This study highlights the need for an aggressive approach towards identifying and treating CV risk in RA patients of South Asian Indian origin who already have an increased risk of CVD. In view of the observation that these RA patients displayed a high prevalence of traditional CV risk factors and metabolic syndrome, it would be rather interesting to compare these findings in a case controlled study in this population.

Chapter 6 - Prevalence of CV risk factors in cases and controls

The prevalence of traditional CV risk factors in patients with rheumatoid arthritis is compared with controls free from inflammatory arthritis in this chapter. Individual risk factors are described in detail.

6.1 Introduction

Rheumatoid arthritis patients have increased incidence of cardiovascular disease which is two times higher when compared to general population (Maradit-Kremers H, 2005). The reasons for this increased CVD event rate associated with RA are likely to be multifactorial and may be related to effects of either treatments or chronic systemic inflammation accelerating atherosclerosis. In general population traditional CV risk factors have been demonstrated to be strong predictors of future CV events (Wilson, 1998). However, the role of traditional CV risk factors is controversial in development of CVD events in association with RA. A study by del Rincon et al found that whilst RA patients had excess CVD events compared to controls this excess was not totally explained by a higher prevalence of CV risk factors. (del Rincon et al., 2001). A further study by this group reported that, in RA, the variance in carotid atherosclerosis, was explained by both traditional CV risk factors and measures of inflammation (del Rincon et al., 2005).Whilst it is likely that in RA disease related factors, such as inflammation, may accelerate atherosclerosis, there is evidence that RA is associated with elevated CV risk factors. A meta analysis suggested that when compared to controls increased prevalence of diabetes, smoking and low HDL cholesterol are found in RA (Boyer et al., 2011). Smoking has been identified as a CV risk factor associated with RA (Saag et

al., 1997, Wolfe, 2000a) and several studies have reported a higher prevalence of smoking in RA cohorts compared to the general population (Maradit-Kremers et al., 2005, McEntegart, 2001, Hutchinson D, 2001, Boyer et al., 2011). However, results from the Nurses health study has not demonstrated any difference in the prevalence of traditional CV risk factor profile in women with and without RA (Solomon et al., 2004).

Dyslipidaemia appears to be more commonly associated with RA but patterns of lipid abnormalities appear to differ between studies (Steiner G, 2009). Active untreated RA appears to influence lipid profile. Whilst several studies have demonstrated lowering of HDL levels in active RA (Park et al., 1999, Kitas, 1997), the effect of disease activity on total cholesterol appears to vary between studies. Some studies have reported disease activity is associated with an increase in total cholesterol (Georgiadis AN, 2006) while others demonstrate that total cholesterol is reduced in active RA (Situnayake and (Kitas, 1997). However, further studies in RA have not identified any associations between disease activity and total cholesterol levels (Choi and Seeger, 2005, Dursunoglu D, 2005). There is also evidence that levels of triglycerides are influenced by RA disease activity. In a US longitudinal study it was observed that triglyceride levels fall in the years prior to diagnosis of RA (Elena Myasoedova and Patrick D Fitz-Gibbon, 2011). Others have suggested that serum triglyceride may reduce in inflammatory autoimmune disease states (Iannello S, 2003). However, others have suggested that triglyceride levels rise in chronic inflammatory states (Sattar et al., 2003)

In addition it seems RA may be associated with abnormal glucose metabolism. Chronic systemic inflammation in RA has been linked to an increased prevalence of insulin resistance (IR) and type 2 Diabetes mellitus (T2DM) (Dessein et al., 2002, Sidiropoulos et al., 2008). However, there is little published data reporting prevalence of type II DM in the context of RA. As type 2 DM and metabolic syndrome are strongly associated with increased CV events this is an important area to study.

Many of the studies of CV risk associated with RA have been conducted in European or American populations of patients. There are to date very few published studies exploring whether CV risk may be increased in South Asian Indian RA patients compared to controls.

South Asian Indians have an increased risk of CVD events which tend to occur at a younger age than that observed in western populations (Enas et al., 1992). This has been estimated to be 5-10 years earlier when compared to Caucasians (Yusuf S, 2004, Teoh, 2007). Indians residing in India have a very high prevalence of traditional CV risk factors. Metabolic syndrome is seen in 25 – 30 % of adult South Asian Indians (Misra A, 2006).

If the prevalence of CV risk factors in the Indian population is very high it is possible that development of RA may increase this risk of CVD even further. Understanding this would be important as the Indian RA patient could be targeted for aggressive CV risk factor modification treatment. However the converse of this could be that in a

population with a very high background prevalence of CV risk factors, development of RA may not further increase the prevalence of elevated CV risk factors.

Case control studies addressing this problem may provide information whether CV risk in Indians is further magnified in the presence of RA. This study was undertaken to compare CV risk factors in RA cases and local population controls free from inflammatory joint disease.

6.2 Aim

The primary aim of this study was to compare the prevalence of elevated traditional CV risk factors in patients with RA to that observed in age and gender matched controls, free from inflammatory arthritis.

6.3 Materials and methods

6.3.1 Patients and controls

This cross-sectional study included consecutive RA patients fulfilling ACR 1987 criteria (Arnett et al., 1988). These RA cases comprised the RA cohort described in chapter 4 section 4.6 and details of inclusion and exclusion criteria and evaluation for these RA patients are described in the methods chapter.

Control patients who were free from inflammatory arthritis were identified and recruited to the study. The controls were frequency matched for age and gender to the cases. RA

cases were encouraged to recommend friends and relatives to take part in the control group for this study. This allowed a degree of matching for both social class and urban dwelling of participants, as the index case of RA was likely to recommend friends or relatives from a similar background to take part in the study. One fourth of the control group participants were hospital staff and their relatives see chapter 4 section 4.8. The control patients were given separate appointments for assessments. All participants were South Asian Indians and no other ethnic groups were included in either the cases or control groups. Details of assessments are described in chapter 4 section 4.9.

6.3.2 Analysis

The distribution of CV risk factors in cases and controls were described. Simple hypothesis testing using the Chi squared test was used to explore whether elevated levels of CV risk factors were more prevalent in cases than controls.

Logistic regression was used to identify whether elevated risk factors were associated with being a case of RA.

6.3.3 Data collection

The RA cases and controls underwent a detailed questionnaire using a standard pro forma, physical examination, and laboratory analysis were performed as described in the methods chapter.

6.3.4 Cardiovascular risk assessment

Traditional CV risk factors were recorded in cases and controls and the 10 year risk of developing a CVD was calculated using Framingham (Wilson, 1998) and JBS risk score (Durrington, 1997) for predicting 10 year risk of a CHD event.. Anthropometric measurements were taken. Details of the evaluations are described in methods chapter 4 section 4.10.

6.4 Results

6.4.1 CVD risk factors in cases and controls

6.4.1.1 General descriptive data

Eight hundred consecutive RA patients fulfilling 1987 ACR criteria and 800 controls free from inflammatory arthritis were recruited. The mean age of RA patients was 46.5 years, 668 (83.5%) were females and 132 (16.5%) were males. In the control group mean age was 47 years and 666 (83.3%) were females. Prevalence of females in the RA group was slightly higher than in the control group. This difference was not statistically significant. Vegetarianism was reported more frequently by participants in the control group i.e. 224 vs 213. General demographics are summarized in Table 6.1. The prevalence of reporting a family history of DM and CVD was similar in the two groups. A family history of hypertension was more frequently reported by the participants with RA than in the control group 29.5% vs 21.8%. Smoking was rarely reported by study participants. Only 12 RA patients (1.5%) and five controls (0.6%) recording a history of current or ever smoking.

Table 6.1 Descriptive data of demographics and co morbidities and blood pressure

Parameters	Description	Cases n=800		Controls n=800	
Demographics					
Age in yrs	med [IQR]	46.5	[38, 55]	47	[37, 55]
Female	n (%)	668	(83.5)	666	(83.3)
Male	n (%)	132	(16.5)	134	(16.7)
Vegetarian	n (%)	213	(26.6)	224	(28.0)
Smoking	n (%)	12	(1.5)	5	(0.6)
Family history					
F. history CVD	n (%)	101	(12.6)	97	(12.1)
F. history DM	n (%)	252	(31.5)	242	(30.3)
F. history HTN	n (%)	236	(29.5)	174	(21.8)
Co morbidities					
Co morbid DM	n (%)	138	(17.3)	57	(7.1)
Co morbid HTN	n (%)	236	(29.5)	174	(21.7)
Co morbid CVD	n (%)	5	(0.6)	0	0
Hypothyroid	n (%)	82	(10.5)	29	(3.6)
Blood pressure					
Systolic mmHg	med [IQR]	130	[120, 140]	130	[12140]
Diastolic mmHg	med [IQR]	80	[80, 90]	80	[80, 90]
Anthropometric measurements					
Waist : Hip ratio	med [IQR]	0.92	[0.86,0.98]	0.91	[0.87, 0.96]
High Waist : Hip ratio *	n (%)	218	(27.5)	183	(22.9)
BMI	med [IQR]	26.1	[23.1,29.7]	26.4	[23.6, 29.4]
BMI >25	n (%)	481	(60.1)	514	(64.3)
Fasting Sugar and lipids					
FBS	med [IQR]	87	[76,102]	84	[77, 91]
T-Chol	med [IQR]	175	[154,201]	168	[153.5,187]
HDL-Chol	med [IQR]	48	[45,51]	47	[44,50]
LDL-Chol	med [IQR]	99	[79.5,120.5]	98	[85,114]
TG	med [IQR]	132.5	[98,184]	114	[90,146]
T-Chol : HDL ratio	med [IQR]	3.7	[3.3,4.2]	3.6	[3.2,4]

F. history- Family history, CVD- Cardiovascular Disease, HTN- Hypertension, DM- Diabetes Mellitus, IQR- Inter quartile range, BMI- Body Mass Index, ,*Waist: Hip ratio classified as high if ≥ 0.95 in Women & if, ≥1 in Men, T-Chol- total cholesterol, HDL-Chol- high density lipoprotein cholesterol, LDL-Chol- low density lipoprotein cholesterol, TG- triglyceride

6.4.2 Co morbidities in cases and controls

Co morbidities were more frequently reported by RA patients. Nearly 30% of the RA cases reported co-morbid hypertension compared to 174 (21.8%) of controls. Median systolic and diastolic blood pressure values were the same in cases and controls. Very few patients or controls had systolic BP below 120 mm Hg which is unusual in a

younger aged predominantly female group. The BP data was not normally distributed and was skewed to the left in the RA cases. 219 RA patients displayed a systolic BP above 140 mm of Hg compared to 201 controls. Diastolic BP above 90 was observed in 39.4% of the RA cohort compared to 34.9% of the controls (see Table 6.4).

Prevalence of co morbid diabetes was particularly high in the RA cases and was reported by (17.3%) of this group. Co morbid DM was fairly prevalent in the control group affecting 57 (7.1%) of control participants. RA patients exhibited a high prevalence of hypothyroidism. It was found to be three times higher in RA 10.5% vs 3.6% in controls. In addition when the numbers of reported co morbidities were examined, 12.5% of the RA cases and 5.5% of controls reported 2 or more co morbidities.

6.4.2.1 Anthropometric measurements

The median waist hip ratio was similar in the two groups. However, when subjects were classified as having a high ratio (defined as ≥ 0.95 in women & ≥ 1 in men), 27% of RA patients compared to 23% of controls had elevated waist hip ratios.

Body mass index was found to be similar in the two groups. It is to be noted that both RA cases and controls had a median BMI in the obese / overweight range (>25 kg/m2).

6.4.2.2 Lipid Profile and fasting blood glucose

Though the median values of blood sugar and lipids were within normal range in both cases and controls the median FBS, T-Chol, HDL-Chol, TG and T-Chol: HDL-Chol ratios were all slightly higher in RA cases.

6.4.2.3 Composite CHD Risk scores

CHD risk scores were calculated for all 800 patients and 800 controls. Median CV risk score as per JBS and Framingham were similar between cases and controls. Using Framingham the 10 year risk of a CHD event was 4%. The CHD risk scores calculated using JBS and based on systolic BP were slightly lower at 3.2% in cases and 2.9% in controls. The JBS CHD risk scores were divided into tertiles (<1.5%, 1.5-<5%, >5%) and slightly more controls had CHD scores in the lowest tertile (see Table 6.2).

Table 6.2 Calculated CHD risk scores in cases and controls

		Patients n = 800		**Controls n = 800**	
	Calculated CHD risk				
Based on Framingham	10 yr CHD risk % med [IQR]	4	1, 8	4	0, 7.5
*Based on JBS	10 yr CHD risk % med [IQR] (systolic)	3.2	[0.9,6.6]	2.9	[0.6, 5.8]
	Tertiles of 10 year CHD % risk (Systolic BP)				
*Based on JBS	<1.5%	257	(32.1)	298	(37.3)
	1.5- <5%	266	(33.3)	248	(31.0)
	>5%	277	(34.6)	254	(31.8)

Calculated 10 year % risk of Coronary Heart Disease (CHD) event using JBS (Joint British societies) CHD risk calculator

6.4.2.4 Metabolic Syndrome

NCEP ATP III (national cholesterol education programme adult treatment panel III) metabolic syndrome (MS) criteria were applied to all cases and controls see Table 6.3. Forty six percent cases met criteria for metabolic syndrome vs 33.4 % in the control group. Only 7.4% of RA cases and 8.1% of controls did not have any criteria for MS.

Table 6.3 Meets criteria for ATPIII metabolic syndrome in cases and controls

		Patients n = 800		**Controls n = 800**	
		n	%	n	%
ATP III score	0	59	7.4	65	8.1
	1	156	19.5	201	25.1
	2	217	27.1	267	33.4
	3	235	29.4	208	26.0
	4	119	14.9	54	6.8
	5	14	1.8	5	0.6
ATPIII	Meets Criteria for MS	368	46.0	267	33.4

6.4.2.5 Elevated CVD risk factors in cases and controls

The CV risk factors were divided into categorical variables and associations between elevated risk factors and RA cases are presented in Table 6.4. These have demonstrated that a significant association between elevated CHD risk scores and RA exists. In addition co morbid DM was significantly elevated in RA cases ($p < 0.001$). A trend for association was observed between elevated diastolic BP (>90 mm of Hg) and RA ($p=0.06$) but no associations were seen with elevated systolic BP defined as (>140 mm of Hg).

After categorization of BMI into two groups, the prevalence of overweight and obesity (BMI >25) was found to be higher in controls (64.3%) vs cases (60.1%) see Table 6.4.

No significant differences were seen with elevated waist hip ratios between cases and controls.

Table 6.4 Prevalence of elevated CVD risk factors in RA cases and controls

CVD Risk factor	RA Cases n=800		Controls n=800		Chi2	p value
	n	%	n	%		
Comorbid Type II DM (Prior diagnosis)	138	17.3	57	7.1	38.2	p<0.001
Smoking (Current smoker)	12	1.5	5	0.6	2.9	p=0.08
Family history CVD	101	12.6	97	12.1	0.09	p=0.76
Systolic BP ≥140 mmHg	219	27.4	201	25.1	1.05	p=0.36
Diastolic BP ≥ 90 mmHg	315	39.4	279	34.9	3.47	p=0.06
High Waist:Hip ratio	451	56.4	443	55.4	0.16	p=0.69
BMI>25	481	60.1	514	64.3	2.9	p=0.09
T-Chol >200mg/dl	203	25.4	84	10.5	1142	p<0.001
HDL- Chol <40mg/dl	47	5.9	31	3.9	3.5	p=0.06
T -Chol:HDL- Chol ratio >4.5	106	13.3	44	5.5	28.3	p<0.001
TG >150mg/dl	319	39.9	176	22.0	59	p<0.001
FBS >100mg/dl	220	27.5	91	11.4	66	p<0.001
FBS in DM range >126 mg/dl	57	7.1	3	0.4	50	p<0.001
Framingham CHD risk >10% n (%)	212	26.5	174	21.8		p<0.001
Framingham CHD risk >15% n (%)	90	11.3	60	7.5		p<0.001
* JBS CHD >10% n (%) (systolic)	125	15.6	69	8.6	18	p<0.001
* JBS CHD >15% n (%) (systolic)	101	12.6	61	7.6	11	p<0.001
** JBS CHD >10% n (%) (diastolic)	59	7.4	18	2.3	22	p<0.001
** JBS CHD >15% n (%) (diastolic)	45	5.6	13	1.6	18	p<0.001

Waist:Hip ratio classified as high if ≥ 0.95 in Women & if, ≥1 in Men), *CHD risk (systolic) elevated CHD risk score based on systolic BP
**CHD risk (diastolic) elevated CHD risk score based on diastolic BP

Differences in the lipid profiles of RA cases and controls were observed. A quarter of the RA patients had high total cholesterol and this proportion was significantly lower than in the control group (10.5%) (p<0.001). Though the numbers of cases with low HDL were slightly more prevalent in the RA group this difference did not reach statistical significance (p=0.06). High triglycerides in RA cohort were almost two times

more prevalent than in controls 39.9 % vs 22% and Chi squared testing revealed a significant association between RA and elevated triglyceride levels ($p<0.001$). The ratio of total cholesterol and HDL cholesterol was found to be two and a half times higher in RA cases compared to controls 13.3% vs 5.5%, again reaching statistical significance ($p<0.001$).

The subjects were classified according to elevated blood glucose levels. Two hundred and twenty RA patients (27.5%) and 91 (11.4%) controls had fasting blood glucose above 100 mg/dl ($p<0.001$). A significant difference was also seen when fasting blood glucose in diabetic range of above 126 mg/dl was taken into consideration with 57 RA patients compared to 3 controls had a blood sugar in the diabetic range ($p<0.001$).

Though the median CHD risk scores were similar in the two groups, elevated levels of CHD risk (>10%) calculated using Framingham and JBS were significantly more prevalent in RA compared to controls. This was also true for high CHD risk (>15%).

6.5 Univariate and age and gender adjusted logistic regression - exploring associations between RA and individual CVD risk factors age and gender adjusted logistic regression in cases and controls

Results of the univariate and age adjusted logistic regression are shown in Table 6.5 and Figure 6.1. Nearly all of the traditional CV risk factors were significantly associated with being an RA case. Increased prevalence of elevated BMI, elevated systolic BP and family history of CHD were not strongly associated. There was nearly a 3 fold increase in odds of Type 2 diabetes in cases of RA compared to controls. When the elevated fasting blood glucose values were compared, elevated fasting blood sugar (>100mg/dl) was strongly associated with RA. However, fasting blood sugar in diabetic range (>126mg/dl) was very strongly associated with RA (OR_{adj} 20.6 (95% CI 6.4, 66.2) in the age and gender adjusted analysis. Despite high prevalence of metabolic syndrome in the control population, metabolic syndrome remained strongly associated with RA (1.8 (OR_{adj} 1.45, 2.23)) in this case control study. A weak association between elevated waist hip ratios was observed, with RA patients having a 20% increased odds of increased waist to hip measurements compared to controls. However, increased BMI was not significantly different between cases and controls.

Whilst smoking was more common in cases of RA, the age and gender adjusted analysis did not reach statistical significance (OR 2.6 (95%CI 0.9, 7.5)).

High diastolic BP (>90 mm of Hg) had a trend for association with being a case of RA and high systolic BP (>140 mm of Hg) did not show any association with RA. Rather interestingly when a high cut off of diastolic BP of more than 95 mm of Hg was used there was a strong association with being a case of RA (OR 3.41(95% CI 2.21, 5.24)).

A strong association between high total cholesterol (>200 mg/dl) and RA was seen. A three fold increased odds of high cholesterol was seen in RA cases (OR 2.9 (95%CI 2.2, 3.9)). The association between low HDL cholesterol and RA was significant but not as marked. However, the prevalence of elevated triglycerides in RA was increased by a factor of 2 (>150mg/dl).

When the composite CHD risk scores were explored, RA was strongly associated with both elevated and high CHD risk scores when calculated with Framingham and JBS. However, the strongest associations were seen with high CHD risk calculated with JBS based on diastolic BP where RA patients had a 4 fold increase, in age and gender adjusted analyses see Table 6.5.

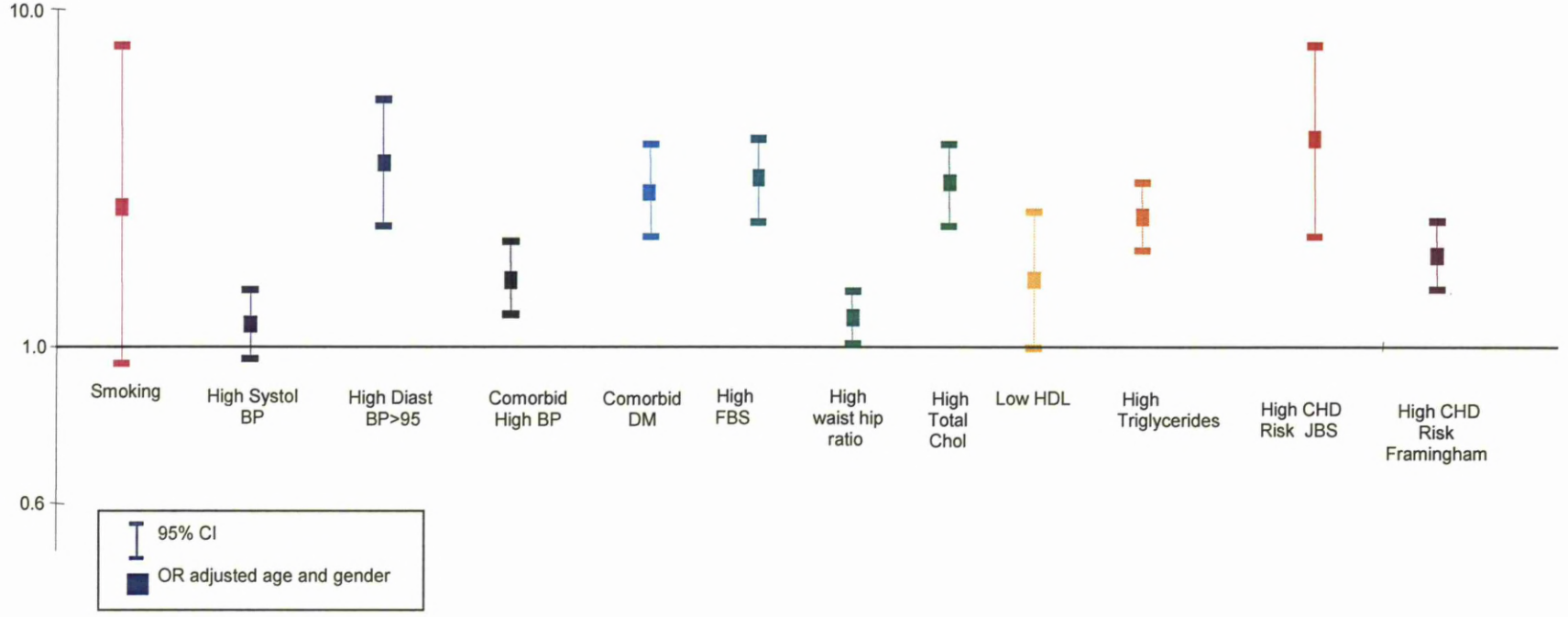
Figure 6.1 demonstrates pictorially the age and gender adjusted associations between individual CV risk factors, CHD risk scores and RA.

Table 6.5 Results of univariate and age and gender adjusted logistic regression-exploring associations between RA and individual CVD risk factors

	RA cases n = 800	Controls n = 800	Univariate		adjusted age & gender	
CVD Risk factor			**OR**	**95% CI**	**OR**	**95% CI**
Co morbid Type II DM	138	57	2.72	1.96, 3.76	2.85	2.05, 3.99
Co morbid Hypertension	236	174	1.5	1.20, 1.89	1.56	1.23, 1.99
Smoking	12	5	2.42	0.84, 6.90	2.58	0.88, 7.54
Family history CVD	425	438	0.94	0.76, 1.14	0.94	0.76, 1.13
Systolic BP ≥140	219	201	1.12	0.89, 1.40	1.13	0.89, 1.44
Diastolic BP ≥ 90	315	279	1.21	0.99, 1.49	1.22	0.99, 1.51
Diastolic BP >=95	91	29	3.41	2.21, 5.24	3.46	2.25, 5.34
High Waist:Hip ratio*	218	183	1.26	1.01, 1.58	1.26	1.01, 1.59
BMI>25	481	514	0.84	0.69, 1.02	0.82	0.67, 1.02
T-Chol >200mg/dl	203	84	2.90	2.19, 3.82	2.96	2.23, 3.91
HDL-Chol <40mg/dl	47	31	1.54	0.97, 2.46	1.56	0.98, 2.48
TG >150mg/dl	319	176	2.35	1.89, 2.93	2.38	1.91, 2.97
FBS >100mg/dl	220	91	2.96	2.26, 3.86	3.07	2.34, 4.03
FBS in DM range >126 mg/dl	57	3	20.4	6.35, 65.4	20.62	6.42, 66.19
Framingham CHD risk>10%	212	174	1.30	1.03, 1.63	1.44	1.10, 1.92
Framingham CHD risk >15%	90	60	1.56	1.12, 2.20	1.72	1.18, 2.50
*10 year CHD risk >10% n (%) (systolic)	101	61	1.75	1.25, 2.44	1.96	1.36, 2.83
*10 year CHD risk >15% n (%) (systolic)	45	13	3.61	1.93, 6.74	4.01	2.10, 7.67
**10 year CHD risk >10% n (%) (diastolic)	125	69	1.96	1.44, 2.68	2.34	1.65, 3.33
**10 year CHD risk >15% n (%) (diastolic)	59	18	3.46	2.02, 5.92	3.91	2.23, 6.84
Meets criteria for MS	368	267	1.70	1.4, 2.1	1.8	1.45, 2.23

High waist hip ratio =Waist hip ratio >1 in males and >0.95 in females

Figure 6.1: CV risk factor associations with RA (logistic regression adjusted for age and gender)



6.6 Discussion

This study has demonstrated that RA patients have a much higher prevalence of elevated CV risk factors when compared to controls. This is particularly interesting given the high background prevalence of CV risk factors in the Indian control population. Therefore it seems that having RA is associated with a significant rise in traditional CV risk factors. This contributed to the higher 10 year CHD risk scores observed in RA patients.

Compared to controls, RA patients had fourfold increased odds of having elevated CHD risk. This finding is important as Indians exhibit increased risk of CVD events at a lower BMI when compared to Caucasians (Misra and Khurana, 2011).

In view of increased prevalence of CV risk factors there is an urgent need for mortality studies in South Asian Indian RA patients. When the individual CV risk factors were analysed separately it is clear that dyslipidaemia, co morbid DM and elevated fasting blood glucose as well as diastolic hypertension were the risk factors most strongly associated with RA. In addition an elevated waist to hip ratio was associated with RA but not increasing BMI. These risk factors all contribute to the metabolic syndrome. Metabolic syndrome was significantly associated with RA. This is interesting given the very high background prevalence of metabolic syndrome in this region of India. The prevalence of metabolic syndrome was high affecting 46% of cases and 33% of controls. This prevalence rate appears very high and other studies of metabolic syndrome in general population of South Asian Indians have reported similar high rates

(Misra A, 2006, Misra and Vikram, 2008, Deepa et al., 2009). A recently reported study from urban and rural districts of West Bengal has reported rates of metabolic syndrome using the ATPIII definition as high as 58% in urban dwelling females (Das, 2011). The fact that having RA was associated with a further 80% increased risk of metabolic syndrome over and above that observed in age, gender and urban dwelling controls is of concern as this group of RA patients appear to be at greatly increased risk of developing type II diabetes as well as being at risk of future CV events.

Rheumatoid cachexia has been identified in patients with active disease. There is abnormal body composition in the form of loss of lean muscle mass and increase in fat mass. These changes may be seen with normal or low BMI. Chronic inflammation in active RA is associated with increase in circulating pro inflammatory cytokines especially tumour necrosis factor alpha which further increases joint inflammation and fatigue causing a reduction in physical activity. The reduced physical activity may be associated in loss of muscle mass. Rheumatoid cachexia is associated with increased visceral fat and increased waist circumference. Rheumatoid cachexia has been observed in 38% of patients with active disease (Engvall et al., 2008). In a review article a possible link of rheumatoid cachexia to increase in CV risk factors, metabolic syndrome and thereby increased risk of CVD has been discussed (Summers et al., 2010).

Dyslipidaemia, with a higher ratio of total cholesterol to HDL cholesterol, was also significantly associated with RA, further contributing to the elevated CHD risk score observed in RA cases compared to controls. In addition, the RA cases had a significantly higher prevalence of elevated triglyceride levels. Whilst dyslipidaemia has

been described in association with RA the pattern of dyslipidaemia that has been observed in this case control study is interesting. Compared to healthy controls we would expect that the RA cohort would have a higher systemic inflammatory burden. Inflammation influences the lipid profile in different way. High levels of inflammation are associated with lowering of HDL cholesterol and active RA has been associated with both low total cholesterol and HDL cholesterol resulting in an unfavourable atherogenic index (White D et al 2006). However in this case control study RA was associated with a significantly higher prevalence of elevated total cholesterol when compared to controls and only modest reduction in HDL. Therefore whilst a strong association between RA and dyslipidaemia defined by the total cholesterol to HDL cholesterol ratio this was largely due to elevation in total cholesterol associated with RA. Possible reasons for this might include the effects of glucocorticosteroid treatment on the lipid profile in RA patients. However, suppression of inflammation by RA treatments is known to improve the lipid profile (Park YB et al 2002). QUEST RA study has demonstrated that 14% of RA patients had dyslipidaemia (Naranjo et al., 2008). Literature on triglyceride is limited but there appears to be an inverse association between inflammatory auto immune disease and triglycerides (Iannello S, 2003) which was not what was observed in this case control study. Possible explanations for this apparent paradoxical rise in triglycerides in RA patients is not clear. This might reflect the effects of RA disease on exercise capacity. We know that hypertriglycerideamia is associated with high fat dietary intake but apart from the slight increase in number of cases that reported vegetarian diets it was not possible to explore dietary differences in any detail between cases and controls. Other factors associated with increased

triglyceride levels include hypothyroidism. The prevalence of hyothyroidism was much higher in RA cases and this could have contributed to the increased prevalence of raised triglycerides. However as most patients were on thyroxine treatment at the time of assessment it is unlikely that this would have increased triglyceride levels to such a degree.

Increased prevalence of elevated triglyceride levels could be related to obesity. Though BMI was similar in the two groups, RA patients had a higher prevalence of high waist: hip ratios. This suggests that RA may be associated with different body composition. Unfortunately measuring body composition was not a part of this study. However, high waist measurements but similar BMI do suggest accumulation of abdominal girth. This usually represents increased fat and may fit with the known association of loss of lean muscle associated with inflammation and RA. This is the picture observed in insulin resistance and this may be the reason for increased DM as part of inflammation associated metabolic syndrome.

It is estimated that India has approximately 32 million diabetics which is projected to increase to 70 million by year 2025 (King et al., 1998). The prevalence of co morbid DM is alarmingly high in our RA population and this study gives an important message for assessing the CV risk factors in RA because according to a survey published in a leading national daily – The Hindu business line (21 Oct 2005) Hyderabad is emerging as the diabetic capital of India. As the study population belongs to this region, even normal controls may display an increased risk of diabetes. Not many studies have

addressed the prevalence of diabetes in patients with rheumatoid arthritis. An association between systemic inflammation and diabetes (Pradhan AD, 2001) and impaired glucose handling in patients with RA has been reported (Svenson KL, 1988). A study in different races in Singapore has demonstrated that mortality due to type 2 DM was higher in Asian Indians when compared to Chinese and Malay population (Ma et al., 2003). The increased prevalence of type 2 diabetes in our population could be due to high prevalence of metabolic syndrome which is known to increase the prevalence of type 2 DM. As RA was active in the cases we also presume them to be less physically active. Possibility of clustering of autoimmune disease was considered but all the participants reporting diabetes had type 2 DM hence autoimmune clustering is not thought to be the reason.

Co morbid hypertension was higher in RA when compared to controls. Increased prevalence of HTN was observed earlier in RA (Panoulas et al., 2007). However this study did not compare the prevalence of hypertension with normal control population. In our cohort elevated diastolic blood pressure was found to be associated with RA and a statistically significant association was seen with the 95 mm Hg cut off for diastolic hypertension. This is in accordance with a previous study which had demonstrated high prevalence of diastolic blood pressure in RA patients (McEntegart, 2001). However, the Nurses health study did not observe such an association (Solomon et al., 2004). Participants in this study were older; also there is no information of disease duration, disease activity and drugs used for the control of RA all of which are known to have an impact on CV risk factors. The effect of gender on CV risk cannot be ruled out.

Hypertension may be related to treatment and in this study more than 60% of patients were treated with NSAIDs. Thirty seven percent of them were on combination of steroids and NSAIDs. A well recognised side effect of NSAIDs is moderate elevation in BP (Armstrong and Malone, 2003). However, as much of this is due to renal effects and salt retention this usually influences systolic BP more than diastolic BP and therefore is unlikely to be responsible for the elevated diastolic BP seen in the RA cases in this study. Another explanation might be pain induced BP rise but rise of BP due to anxiety is usually in systolic blood pressure and we cannot explain the diastolic rise in blood pressure in our RA cohort. Another cause of hypertension could be renal impairment. Though this study did not include testing renal parameters but as a routine clinical practice all patients on treatment undergo regular renal and liver function testing once in three months.

The effects of drugs in causing hypertension cannot be ruled out. Patients in the RA cohort using glucocorticoids were on physiological dose (<7.5mg/day). Low dose corticosteroids have a week association with CV risk factors in a dose related manner (Adeline Ruyssen-Witranda, 2011). Low dose steroids may have a cardio protective effect by their anti inflammatory and anti proliferative effect on the vessel wall (Bartoloni et al., 2011). Sixteen percent of RA patients in this study were on leflunomide which is known to elevate blood pressure. There are no reports regarding a selective diastolic rise in blood pressure seen with this drug. The exact reason for this diastolic hypertension is not clear. Further studies are needed addressing hypertension in RA.

Hypothyroidism is associated with increased risk of CVD in the general population (Walsh JP, 2005). Co morbid hypothyroidism in this study was significantly higher in cases when compared to controls. Our finding is in accordance with published literature that prevalence of hypothyroidism in more in RA patients (H G Raterman, 2008). The increased prevalence of hypothyroidism in RA may be due to autoimmune clustering and may be referred to as "disease pyramid theory". A study has demonstrated that RA may accelerate progression of subclinical hypothyroidism into clinical hypothyroidism (Chan et al., 2001).

Recent literature states that presence of RA is an additional risk factor for CVD like DM (Peters et al., 2009). Hence, this South Asian Indian RA population is at a further magnified risk of CVD in view of the prevalent co morbidities.

Prevalence of vegetarianism being more in females may be because Indian females follow religious and social customs more than the male population. There was no significant difference between cases and controls regarding the use of vegetarian diet. This is in accordance with recently published literature that there is no association between RA risk and the consumption of non vegetarian diet (Benito-Garcia et al., 2007). This is cross sectional data and diet may be modified after RA has developed.

Smoking was reported very infrequently in this study. This may reflect the fact that the populations consisted of a large proportion of female middle class participants and in this demographic smoking in females is considered a taboo in many Indian families.

Most of the studies in RA addressing CV risk are conducted in European or American populations and report a much higher prevalence of smoking. The QUEST RA study conducted at 48 sites in 15 countries across Europe and USA including 4,363 patients reported current smoking in 26% male and 15% females (Naranjo et al., 2008). However, despite the very low prevalence of current smoking in this study we still detected a higher prevalence of smokers in the RA cohort.

There appears to be an inverse relationship between RA and lipids. Active RA is associated with low total cholesterol and HDL cholesterol resulting in an unfavourable atherogenic index (White et al., 2006). Suppression of inflammation by RA treatments is known to improve lipid profile (Park et al., 2002). The QUEST RA study has demonstrated that 14% of RA patients had dyslipidaemia (Naranjo et al., 2008). Literature on triglyceride is limited but there appears to be an inverse association between disease activity and triglycerides.

Dyslipidaemia in South Asians Indians is about 20 – 30 % in various studies. Two studies from Andhra Pradesh have reported a prevalence of hypercholesterolemia of 18.5% and 31% (Reddy KK et al 2002, Reddy NK et al 2002). Compared to Caucasians South Asian Indians tend to have high triglyceride and low HDL (Anand et al., 2000). When compared to prevalent dyslipidaemia in the background normal population, RA patients in this study have demonstrated more than three times increased odds of having elevated total cholesterol, more than two times increased odds of having elevated triglycerides and one and a half times the odd of having low HDL cholesterol. The

dyslipidaemia observed could be due to active RA. Compared to controls the RA cohort had fourfold increased odds of having elevated CHD risk score.

Patients in the RA cohort had active disease and were on treatment with NSAIDs, steroids and DMARDs. Our cohort represents the setting of a specialist tertiary care centre where patients with active disease consult rheumatologist for disease control. Our cohort does not represent patients who have very mild disease which is controlled by non specialists or by other systems of medicine such as Ayurveda, Homeopathy, Unani, Naturopathy and Herbal medicines, which are used by patients in developing countries.

This is the largest case control study in South Asian Indian patients. We have generated a database which will be helpful in comparing the RA cases and controls and plan to look at different aspects in future studies.

The weakness of our study is that we were unable to accurately assess fasting lipid samples although blood glucose was measured after an overnight fast. We were also unable to record the use of over the counter medicines especially NSAIDs. However, when the control population was included care was taken in asking and examining for the presence of joint pains. Hence we presume that the patients were not on high dose NSAIDs.

India is in the middle of a CAD epidemic. Asian Indians have demonstrated CAD rates which are 50 to 400 times higher than individuals of other ethnic origins and at least

four times that of Caucasians (Enas, 2001). Asian Indians are at an increased risk of developing CAD and diabetes which occurs at least 10 years earlier when compared to other populations. The world health organization has predicted CVD to be a major cause of morbidity and mortality in the world and South East Asians are expected to be the most effected among all ethnic populations (Lancet Series on Health in Southeast Asia,25Jan2011).WHOJanuary2011 (http://www.who.int/nmh/publications/9789241597418/en/index.html).

Most of the published studies are in Caucasian RA patients. There may be a genetic influence on the CV risk factors as South Asian Indians are a genetically challenged ethnic group. Compared to RA studies performed in US and European populations this South Asian Indian study has demonstrated that RA seems to be strongly associated with an increased prevalence of traditional CVD risk factors and appears to be particularly associated with type 2 DM . We propose screening and treating modifiable CVD risk factors in RA patients is even more important in South Asian Indian patients. It appears that compared to the background population they have a 2-3 fold increase in prevalence of elevated CHD risk. As the prevalence of CVD is high in the background population this increased CV risk associated with RA is likely to lead to increased CV events in these patients. The median age of this cohort was relatively young and therefore these patients may benefit greatly from risk factor reduction in an attempt to reduce CVD events in the future. There is an urgent need for preventive strategies in South Asian Indian RA patients in the form of physician awareness, patient education, lifestyle modification, aggressive control of RA and institution of reduction of dyslipidaemia in the form of statins. Co morbid hypertension and diabetes should be

addressed and the treating rheumatologist should routinely check patient's blood pressure at every clinic visit and blood glucose should be monitored frequently. The Cochrane review of preventive strategies has found that preventive strategies are helpful in persons with pre existing disease such as hypertension and diabetes in the form of better adherence to therapy (Ebrahim et al., 2011). Since our RA cases had a high prevalence of co morbid conditions there is a possibility of preventive strategies to be effective. Evaluation of lipid profile and CV risk assessment should become a routine practice in all patients annually. In patients with low risk the evaluation can be done less frequently, once in two to three years (Peters et al., 2010). As there are no recommendations for South Asian Indian RA patients the recommendations set by the EULAR standing committee for clinical affairs may be followed until local recommendations are available for Indian patients.

Our study highlights the importance of an aggressive approach towards identifying and treating CV risk in RA patients of South Asian Indian origin who already have an increased risk of CVD

Whilst this cross sectional study has identified that RA is associated with increased CV risk in a South Asian Indian population, little is known about CVD event rates in Indian RA cohorts. It will be interesting to follow these patients up to explore whether rates of events are increased compared to the background rate. However, interventions to reduce CV risk factors that were identified as part of this study may influence future CV event rates.

Chapter 7 - Association of traditional cardiovascular risk factors with rheumatoid disease activity.

The traditional cardiovascular disease risk factors in patients with rheumatoid arthritis are studied in relation to disease activity and associations between CV risk and level of disease activity are explored.

7.1 Introduction

The cause for increased CVD associated with RA is unknown, but is likely to be due to a number of factors including raised traditional cardiovascular (CV) risk factors, inflammation, effects of medication, and reduced capacity to exercise (Boyer et al., 2011, Wallberg-Jonsson et al., 1999, Atzeni, 2010). We have already demonstrated that traditional cardiovascular risk factors are elevated in RA patients compared to controls (see results chapter 5).

When considering CV risk in RA, some authors advocate using traditional CV risk factor scores such as Framingham (Wilson, 1998), SCORE (Conroy RM, 2003) or JBS (Durrington, 1997), but then applying a RA associated weighting to adjust the final CV risk value by applying a 1.5 multiplication factor which should be used when disease duration is more than 10 years, RF or anti CCP is positive, presence of extra-articular manifestations. The patient should meet two out of the three criteria (Peters et al., 2010). QRISK is the new CV risk calculator (Julia Hippisley-Cox, 2007). However, as levels of CV risk factors may be modified by the active disease process in RA this

approach might be too simplistic and may lead to inaccurate estimation of CV risk in RA.

CV risk factors may be modified in states of high inflammation. There is substantial evidence for an association between inflammation and dyslipidaemia. Several studies have suggested that high inflammatory states in RA are associated with lowering of total cholesterol (Situnake (Kitas, 1997, Munro R, 1997, Park et al., 2002, Nurmohamed and Dijkmans, 2009, Boyer et al., 2011) . In a more detailed review Sattar describes how the lipid profile is typically influenced in association with inflammation (Sattar et al., 2003). The characteristic changes of inflammation include lowering of total cholesterol (T Chol), high density lipoprotein (HDL) and triglyceride (TG) levels. In particular levels of HDL cholesterol are disproportionately lowered. So whilst the total cholesterol is reduced in association with inflammation, the marked lowering of HDL in relation to total cholesterol leads to an unfavourable atherogenic index.

However, in the general population, chronic low grade inflammation has also been identified as a predictor of future CVD events. Ridker et al found that in apparently healthy men the value of CRP can predict myocardial infarction and stroke (Ridker et al., 1997). Systemic inflammation is said to play a role in all the stages, including initiation, formation and rupture of atherosclerotic plaques by various mechanisms (Pasceri, 1999). Markers of inflammation are strongly associated with RA in the form of sub clinical atherosclerosis which can be determined by arterial wall thickening, arterial wall stiffness and reduced flow mediated dilatation (del Rincon et al., 2005,

Nagata-Sakurai M, 2003) A study by del Rincon et al looking at the contribution of CV risk factors and RA disease to the development of atherosclerosis observed that atherosclerosis correlated with RA disease duration. CV risk factors and RA disease activity contribute to the development of atherosclerosis and may modify each other (del Rincon et al., 2005). Another study by the same group confirmed the association of systemic inflammation and CV risk factors with atherosclerosis (del Rincón I, 2007). There is also a hypothesis that inflammation may make atherosclerotic plaque unstable and more prone to rupture resulting in myocardial infarction.

In addition, high levels of disease activity in RA may influence the CV system through other mechanisms. When RA is active, physical activity is likely to decline. Reduced cardiovascular fitness may therefore be a contributing factor to the increased CV events seen in RA cohorts as well as contributing to weight gain.

Another important factor to consider is the effect of concomitant medications on the cardiovascular system. When RA disease is active, patients may take more medicines that alter their CV risk factors and influence the vasculature. Use of glucocorticoids may exacerbate fluid retention, hypertension and impair glucose tolerance, causing DM. (Andrews and Walker, 1999, Whitworth et al., 2000). However, use of these drugs to suppress disease activity in RA, may increase activity levels as well as reducing systemic inflammation. With regard to the cardiovascular system the dose of glucocorticoids may be important. In a study by Toms et al, in RA patients, low (<7.5mg/day) and medium dose (>7.5 mg/day) prednisolone use was not associated

with metabolic syndrome, hypertension or lipid abnormalities. The authors concluded that this could be due to beneficial effects of steroids in suppressing inflammation (Toms et al., 2008). Therefore, whilst it is likely that glucocorticoids influence CV risk factors their effective suppression of disease activity in RA may lead to a neutral effect on CVD events in RA.

Use of NSAIDs may also influence CV risk factors by causing hypertension and fluid retention. These drugs tend to be used more during active disease, for additional symptom relief. In addition, some NSAIDs may have a prothrombotic effect and there is some evidence that they may exacerbate heart failure (Gys`ele S. Bleumink, 2003). Observational studies have demonstrated that both selective COX2 inhibitors as well as non COX2 selective NSAID use is associated with increased prevalence of CV events in the general population (Hippisley-Cox J, 2005, Chan, 2006).

In RA, CV events may be increased as a result of the effect of inflammation on CV risk factors, vascular endothelium or a mixture of both. Therefore it is important to understand the effect of high disease activity in RA on CV risk factors.

South Asian Indians have a high prevalence of traditional CV risk factors (Misra and Vikram, 2004). We have demonstrated in the case control study reported in results chapter 6 section 6.4 that RA patients have marked elevation of CVD risk factors associated with metabolic syndrome compared to controls from the same population. Studies have demonstrated that the South Asian Indian population has an increased

incidence of metabolic syndrome, dyslipidaemia and premature atherosclerosis. The WHO (2002) has reported that by 2020 CVD will be a major cause of death and disability in south Asians and nearly half of the deaths will be in young and middle aged South Asian population (WHO report 2002). The high prevalence of metabolic syndrome in Asian Indians with RA is of particular interest as metabolic syndrome is associated with a high inflammatory burden. It is possible that chronic inflammation may promote central obesity and metabolic syndrome further contributing to acceleration of CV risk in RA patients with high disease activity.

Therefore it is clear that the associations between inflammation, CV risk and the development of CVD events is complicated.

7.2 Aim

This cross sectional study was conducted to explore whether elevated disease activity is associated with elevated CV risk factors in a South Asian Indian population of RA patients.

The primary aim was to explore whether the 10 year risk of CVD by Framingham risk score and Joint British Societies risk score of CVD was associated with high disease activity, measured using a DAS 28 score.

The secondary aim was to explore which individual CVD risk factors are associated with elevated disease activity.

7.3 Materials and methods

The eight hundred consecutive adult RA patients fulfilling 1987 ACR criteria (Arnett et al., 1988) and willing to participate in this study were recruited as described in Chapter 4 section 4.7 and used in this analysis.

Joint evaluation was performed by URKR or FF. Disease activity score(DAS28)was calculated using a 28 tender joint count, a 28 swollen joint count, pain visual analogue scale and ESR (Prevoo et al., 1995). The EULAR has set up guidelines for categorising disease activity in RA as low, moderate or high, based on DAS28 score (Alfons and Michiel online DAS calculator). The cut offs for these categories are shown in Table 7. 1. For this study, the patients were classified into two groups depending on their DAS 28. Patients with a DAS 28 of less than or equal to 5.1 formed the moderate/ low disease activity group and patients with a DAS 28 more than 5.1 were classified as being in the high disease activity group.

Table 7.1 EULAR response criteria (J. Fransen, 2005)

Low DAS	Moderate DAS	High DAS
< 3.2	3.2 - ≤5.1	>5.1

CV risk prediction scores to predict ten year risk of CHD events were calculated using the 10 year Framingham coronary heart disease risk score and Joint British Societies (JBS) CHD risk assessor as described in chapter 4 section 4.16. Patients were categorised as having elevated CHD risk if their 10 year Framingham CHD risk score or

JBS score was greater than 10%, and high risk if the Framingham or JBS risk score was greater or equal to 15%.

The ATPIII criteria of metabolic syndrome were applied to all patients and the individuals meeting the criteria were identified. For criteria of metabolic syndrome see methods chapter 4 section 4.17.

Elevated T-Chol was defined as T-Chol ≥200 mg/dl, Low HDL-Chol was defined as HDL < 40 mg/dl, high TG was defined as TG > 150 mg/dl, high LDL-Chol was defined as LDL >160 mg/dl (III, 2002). High BMI was classified as a BMI >25 which corresponds to overweight as per WHO guidelines (WHO, 1995).

7.4 Analysis

The data was analysed using simple descriptive statistics. Categorical variables were described as number (n) and percentage (%). Continuous data was described as median and inter quartile range [IQR]. The composite 10 year risk of a CHD event was calculated by Framingham and JBS risk scores was treated as continuous and categorical variables.

The associations between high DAS 28 and CV risk factors were studied with univariate and age and gender adjusted logistic regression.

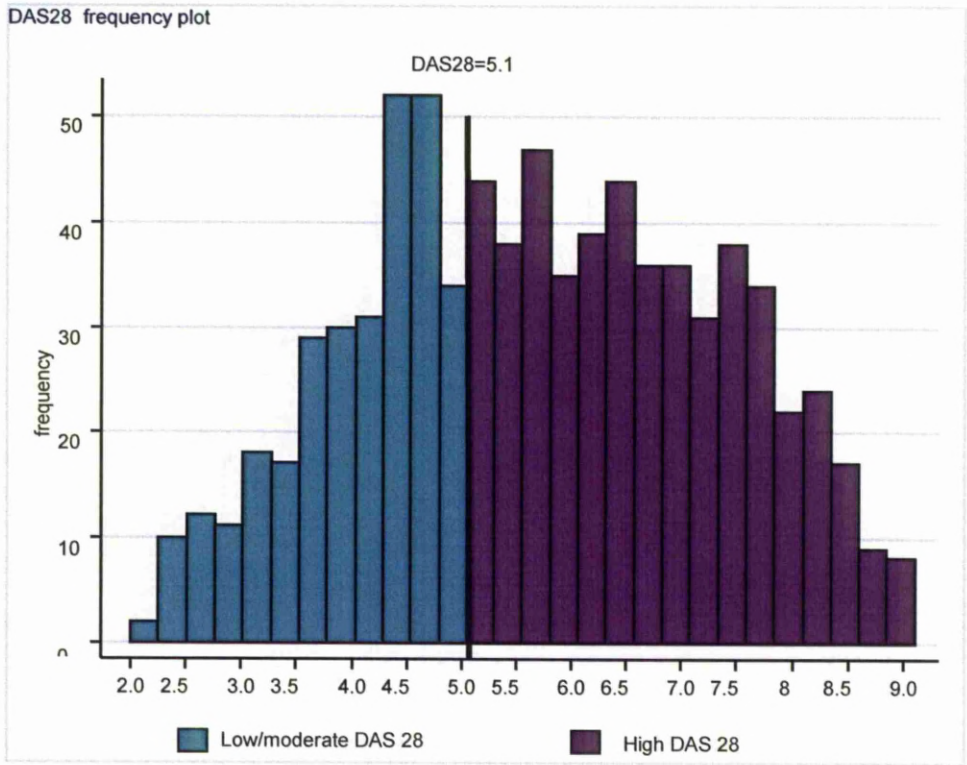
7.5 Results

The data from the cohort of 800 consecutive RA patients was examined. Their characteristics are presented in Table 5.2 and 5.4 in chapter 5- Prevalence of traditional CV risk factors in RA.

Figure 7.1 shows the distribution of DAS scores within the two groups. DAS 28 scores for this cohort were high, with 59% having a DAS 28 in excess of 5.1. These were classified as having high disease activity (high DAS).

There were 322 patients in the low/moderate disease activity group vs 478 in the high DAS group. The stratified baseline characteristics are presented in Table 7.2. The median age of individuals in the high DAS group was 47 years and 46 years in the low/moderate DAS group. The high DAS group had more females, they were older and there were fewer vegetarians. There were more smokers in the high DAS group compared to the low/moderate DAS group (9 vs 3). Co morbid diabetes, hypertension and hypothyroidism were also more frequently observed in the high DAS group. Laboratory parameters such as FBS, T-Chol, HDL-Chol and LDL cholesterol (LDL-Chol) were similar in the two groups. However, the low/ moderate DAS group had marginally higher TG levels compared to the high DAS group (142 vs 129).

Figure 7.1 Bar chart indicating range of DAS 28 scores



The median CHD risk scores were low in both DAS stratified groups but were marginally higher in those with higher DAS. The prevalence of metabolic syndrome (MS) was high in both DAS groups. This was observed in 47% of the low/moderate DAS group and 45 % of the High DAS group.

Table 7.2 Exploring associations between disease activity and cardiovascular risk factors.

Parameter		DAS28 <=5.1 n= 322	DAS28>5.1 n= 478
Gender, female, n (%)	n (%)	263 (81.7)	405 (84.7)
Age in yrs, med [IQR]	med [IQR]	46[38,55]	47 [39,55]
RA duration med [IQR]	med [IQR]	4 [2,10]	4 [1,9]
Vegetarian n (%)	n (%)	91 (28.3)	122 (25.5)
RF positive n (%)	n (%)	242 (75.2)	387 (80.1)
Smoking n (%)	n (%)	3 (0.9)	9 (1.9)
No FH CVD n (%)	n (%)	160 (49.7)	265 (55.4)
Co morbid diabetes	n (%)	52 (16.5)	86 (18.0)
Co morbid hypertension	n (%)	93 (28.8)	143 (29.9)
Co morbid CVD	n (%)	48 (14.9)	49 (10.3)
Co morbid hypothyroid	n (%)	30 (9.3)	52 (10.9)
BP Systolic	med [IQR]	130 [120,140]	130[120,140]
BP Diastolic	med [IQR]	80 [80,90]	80 [80,90]
Waist cm	med [IQR]	94 [86,101]	93 [85,100]
Hip cm	med [IQR]	102 [96,109]	100 [93,108]
Waist/Hip ratio	med [IQR]	0.92 [0.86,0.97]	0.92 [0.86,0.98]
BMI mg/dL	med [IQR]	26.3 [23.4,29.9]	25.6 [23.0,29.6]
FBS mg/dL	med [IQR]	84 [76,102]	88 [78,102]
T-Chol mg/dL	med [IQR]	3.7 [3.3,4.2]	3.7 [3.3,4.2]
HDL-Chol mg/dL	med [IQR]	48 [45,51]	48 [44,51]
LDL-Chol mg/dL	med [IQR]	98 [78,120]	99 [81,121]
TG mg/dL	med [IQR]	142 [103,187]	129 [95,182]
T-Chol / HDL-Chol ratio	med [IQR]	3.7 [3.3,4.2]	3.7 [3.3,4.2]
CHD risk scores			
Framingham 10 yr risk %	med [IQR]	4 [0,8]	4 [2,10]
JBS CHD 10 yr risk % (systolic)	med [IQR]	3.1 [0.7,6.6]	3.4 [1.1,6.6]
JBS CHD 10 yr risk % (diastolic)	med [IQR]	3.2 [0.6,7.2]	3.8 [1.1, 7.3]
Meets criteria for MS	n (%)	151 (46.9)	217 (45.4)

7.5.1 RA disease activity

RA disease duration was similar in the two groups Table 7.3. The high disease activity group had more rheumatoid factor positive patients (80.1% vs 75.2%). As is expected the high DAS group had higher disease activity parameters including 28 joint counts, global VAS and ESR. The median DAS in low/moderate DAS group was 4.3 vs 6.6 in

high DAS group. Only 45 patients in the low/moderate DAS group were in low disease activity (<3.2) Figure 7.1.

Table 7.3 RA disease variables stratified by disease activity

Parameter	Description	Low/moderate disease activity		High disease activity	
		DAS 28≤5.1		DAS 28 >5.1	
RA duration (yrs)	med [IQR]	04	[2,10]	04	[1,9]
RF positive	n (%)	242	(75)	387	(80.1)
SJC	med [IQR]	02	[0,3]	07	[4,14]
TJC	med [IQR]	04	[0,3]	14	[9,22]
Global VAS	med [IQR]	40	[25,50]	83	[60,100]
ESR mm/hr	med [IQR]	41	[35,55]	75	[59,100]
DAS 28	med [IQR]	4.3	[3.6, 4.7]	6.6	[5.8,7.5]

7.5.2 Medication used to treat inflammation

Steroid usage in the high DAS group was more than two times that of the low/moderate DAS group, with 54% reporting use compared to 23%. In the high DAS group 94.4% were current NSAID users. NSAID use was much lower in the low/moderate DAS group where only 31% reported current use. The biologic response modifier etanercept was only used by 2.5% of the low/moderate DAS group vs 5.2% in the high DAS group. The usage of NSAIDS and steroids together was three and a half times higher in the high DAS group. Methotrexate use was high with over 90% using methotrexate in both DAS groups. Both DAS groups had much lower use of other non biologic DMARDS like sulphasalazine, hydroxychloroquine and leflunomide.

Table 7.4 Medications used by patients in the two groups

Medication	Low/moderate DAS group DAS28 ≤5.1		High DAS group DAS28 >5.1	
Steroid use n (%)	73	22.7	261	54.6
Methotrexate n (%)	292	90.7	441	92.3
Sulphasalazine n (%)	28	8.7	31	6.5
Leflunomide n (%)	59	18.3	71	14.9
Hydroxychloroquine n (%)	71	22.1	77	16.1
Etanercept n (%)	8	2.5	25	5.2
NSAIDs n (%)	100	31.1	451	94.4
Steroids & NSAIDs n (%)	45	14.0	257	53.8

7.5.3 Association between DAS 28 and CV risk factors

The associations between CV risk and high disease activity are presented in Table 7.5. No statistically significant associations were observed between high disease activity and the elevated or high composite CHD risk scores (Framingham and JBS). High Framingham CHD risk score and high DAS had a trend for an inverse association (OR adj 0.76 (95%CI 0.46, 1.23)), but this did not reach statistical significance. There appeared to be a trend for a lower prevalence for metabolic syndrome in patients with high DAS 28 (OR adj 0.86 (95% CI 0.69, 1.17)), but again this did not reach statistical significance.

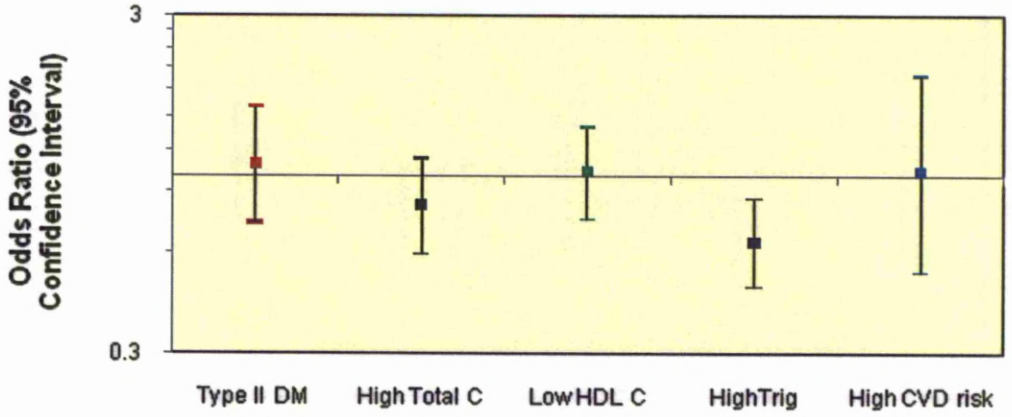
When the individual CV risk factors were analysed, the only risk factors observed to have significant association with disease activity was Triglyceride (TG). However, this was an inverse association, with high DAS being associated with lower TG levels. This association remained significant after adjusting for age and gender (OR adj 0.70 (95%CI 0.52, 0.94)). No significant associations were observed between disease activity and other lipid components (figure7.2).

Table 7.5 Associations between DAS 28 and CVD risk factors

			Univariate		adjusted age & gender	
CVD Risk factor	**DAS 28 ≤5.1 n=322**	**HighDAS28 >5.1n=478**	**OR**	**95% CI**	**OR**	**95% CI**
	n(%)	n(%)				
Co morbid DM	52 (16.2)	86(18.0)	1.34	0.78, 1.66	1.13	0.76,1.67
Co morbid HTN	93 (28.9)	143(29.9)	1.05	0.77, 1.43	1.02	0.73,1.42
Smoking	3 (0.9)	9(1.9)	2.00	0.55, 7.60	2.61	0.67,10.1
F H CVD	160(49.7)	265(55.4)	1.26	0.95, 1.67	1.25	0.94,1.67
Systolic BP ≥140	93 (28.9)	12(26.4)	0.88	0.64, 1.21	0.85	0.60,1.18
Diastolic BP ≥ 90	119(37.0)	196(41.0)	0.98	0.63, 1.52	0.97	0.62,1.52
High Waist:Hip ratio	81(25.12)	137(28.7)	1.20	0.87, 1.64	1.17	0.85,1.62
BMI>25 (%)	200(62.1)	280(58.8)	0.87	0.65, 1.16	0.82	0.61,1.11
T Chol >200mg/dl	86(26.7)	117(24.5)	0.89	0.64, 1.22	0.86	0.62,1.20
HDL Chol <40mg/dl	13(4.0)	34(7.1)	1.82	0.95, 3.51	1.87	0.97,3.62
TG >150mg/dl	143(44.4)	176(36.8)	0.72	0.55, 0.97	0.70	0.52,0.94
LDL chol > 160 mg/dl	16(5.0)	24(5.0)	1.01	0.53, 1.93	1.00	0.52.1.92
High T Chol:HDL ratio	3 (0.9	5 (1.1)	1.12	0.26, 4.74	1.13	0.27, 4.77
FBS>100mg/dl	85(26.4)	135(28.2)	1.10	0.80, 1.51	1.09	0.78,1.51
FBS in DM range >126 mg/dl	20(6.2)	37(7.7)	1.26	0.72, 2.23	1.26	0.72, 2.23
Framingham risk >=10%	84(26.1)	128(26.8)	1.03	0.75, 1.42	1.00	0.67, 1.48
Framingham risk >=15%	41(12.7)	49(10.3)	0.78	0.50, 1.22	0.76	0.46, 1.23
JBS risk >10% (systolic BP)	38(11.8)	63(13.2)	1.13	0.74, 1.74	1.15	0.71, 1.86
JBS CHD >10% (diastolic BP)	50(15.5)	75(15.7)	1.01	0.69, 1.49	0.99	0.63, 1.56
JBS CHD >15% (systolic BP)	18(5.6)	27(5.7)	1.01	0.55, 1.87	1.02	0.53, 1.96
JBS CHD >15% (diastolic BP)	25 (7.8)	34 (7.1)	0.91	0.53, 1.56	0.88	0.49, 1.56
Meets criteria for M S	151(46.9)	217(45.4)	0.94	0.71, 1.25	0.86	0.64, 1.17

There appeared to be an inverse association between blood pressure (especially systolic BP) and high disease activity, though this difference was not statistically significant. Low/moderate DAS patients displayed a tendency for having an elevated BMI in the overweight and obese category (BMI≥ 25).

Figure 7.2 CVD risk factor association with DAS score >5.1 adjusted for age and gender.



7.6 Discussion

This cross-sectional study has not observed any association between the composite CV risk scores and high DAS in this cohort of patients with RA. However, when the traditional CV risk factors were analysed separately, a significant association between high disease activity and low TG levels was observed. The other lipid measurements were not significantly associated with disease activity though there was a trend for lower HDL in the high disease activity group. Other risk factors were similar across the two DAS28 groups.

The finding that the composite CV risk score, using both Framingham and JBS were similar in the two groups was surprising, as our prior hypothesis was that CV risk would be reduced in higher inflammation and high disease activity states as inflammation is associated with reduction in total cholesterol and HDL cholesterol (Sattar et al., 2003).

In this study we did not observe any association between HDL or Total cholesterol with high DAS. However, this lack of association might reflect the moderately high disease activity in the low/moderate DAS comparator group. The median DAS28 in the comparator group was 4.3. Only 14% were in low disease activity, and of these only 5 patients were in DAS28 remission. Therefore, it may be that CV risk modification in association with disease activity actually occurs at moderate levels of disease activity. A study in stable coronary artery disease (CAD) patients has demonstrated that very low level inflammation was associated with dyslipidaemia (Marz W and Bracker, 2004). In the CAD study, the median CRP, measured using high sensitivity assays, was reported as being 3mg/L with an interquartile range between 2 and 8 mg/L. This represents a very low level of inflammation and is very different to that observed in the RA cohort where the lowest ESR was above 30mm/Hr. Unfortunately, the number of RA patients with low DAS28 scores was too small to perform subgroup analyses to test whether low DAS28 was associated with CV risk or dyslipidaemia.

The only significant association observed in this study was between high triglyceride and lower levels of disease activity. As the composite CV risk score is not calculated using triglycerides it is not surprising that the CHD risk scores were observed to be so similar in the two DAS groups.

The finding regarding triglycerides and disease activity is interesting as it is counterintuitive. In the presence of active inflammation there is an increase in

circulating pro inflammatory cytokines especially TNF alpha which increases hepatic lipogenesis causing hypertriglyceridaemia (Feingold et al., 1989).

We would therefore have expected triglycerides to be higher in inflammation and this has been described in studies of patients without RA but with known CAD (Marz W and Bracker, 2004) . The reason for increased triglyceride levels in the low/ moderate disease activity group is not known. It is reported that glucocorticosteroid use increases triglycerides. However, the high DAS group reported more prednisolone use than the low/moderate DAS group so it is unlikely that the difference in triglyceride levels was due to different prednisolone use in this study. The effect of RA disease activity on triglycerides needs to be studied further.

One potential explanation for this anomalous result may be the fact that participants for this study were not fully fasted for accurate assessment of triglyceride levels. Current recommendations suggest a 9-12 hour fast for fasted lipid assessment. http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf. It was not possible for many patients to adhere to this in this study and we were unable to request further fasted samples because of time and financial constraints. Therefore the disease activity associated difference in triglyceride levels may simply reflect reduced appetite observed in patients with very active RA. The raised TG levels further emphasize the importance of lifestyle modification in Indians who are more prone to increased CV risk. The HDL and total cholesterol levels do not require a fasted sample and these values were not seen to differ with disease activity. This was unexpected, as many studies have reported

inflammation and disease activity associated dyslipidaemia. A study by Hadda et al (Hadda V., 2007) in 90 RA patients with active disease (mean DAS28 was 4.9) and mean disease duration of 5.5 years, observed that 38.5% of participants had dyslipidaemia. At baseline low HDL was observed in 34.3%, 4.2% had low total cholesterol and high triglycerides were seen in 4.2%. This study excluded patients with diabetes. The same patients had their lipid profile measured after starting traditional DMARD therapies (methotrexate or sulphasalazine) steroids and NSAIDs. When the patients were evaluated after 8-12 weeks it was observed that there was a small but statistically significant improvement in HDL cholesterol ($p<0.008$). They observed only modest improvement in DAS 28 score with the mean score after treatment being 4.4. It is interesting to note that in my study, the difference in DAS28 scores between the two DAS groups was of a similar magnitude to the improvement in DAS scores observed in Hadda's study, but I did not observe any significant association between DAS and HDL-Chol. Another small study from Jaipur (n=25) reported lower lipid levels and negative correlation of lipids with disease activity (Ghosh et al., 2009). However in my study the number of RA patients was much larger, but the difference in disease activity was modest between the two DAS groups and very few of our comparator group were in a low disease activity state.

One of the strengths of my study is the large number of patients studied. This allowed me to explore associations between DAS group and the whole CV risk profile as well as look at the CHD risk assessments. To my knowledge this is the largest number of RA patients in India who had their CV risk assessment done.

The RA cohort was quite heterogeneous in that we studied patients with wide variation in disease duration (Bjornadal L, 2002). As the risk of CHD events rise appears to rise with increasing RA disease duration even after adjustment for age disease duration. We did not explore whether increased duration of RA influenced CV risk. If this was the case in my cohort we could have adjusted the associations between disease activity and CV risk factors for disease duration at time of assessment.

Another weakness of my study was the examination of a large number of CV risk factors with DAS group. This multiple hypothesis testing approach may have led to a type 1 error, where significance is falsely assigned to an association due to a chance event. The only significant association that was detected was that between elevated triglycerides and lower DAS. Whilst it is possible that this was a chance finding the strength of association was strong and the level of significance for this association was high ($p < 0.01$). This association should be tested in other Asian Indian RA cohorts to explore whether a true association exists between DAS and triglycerides.

Another weakness is that whilst I set out to explore whether CV risk was influenced by high disease activity the comparator lower disease activity group had a median DAS of 4.3 and only 45 patients had low DAS (<3.2) as per EULAR guidelines. As there were so few patients in low disease activity it is possible that comparing CV risk in moderate disease activity with high disease activity would make it more difficult to detect any

difference in levels of CV risk. It would be interesting to study patients with active disease and compare them with patients in remission or low disease activity.

Other studies have commented that inflammation, even at low levels, influences lipid profiles (Sattar et al., 2003). However, if as in my group, all patients studied had moderate or high disease activity it is likely that the inflammatory burden would be great enough, even in the lower DAS group, to influences lipid profiles. In a review article Sattar et al (Sattar et al., 2003) described the lipid pattern associated with RA as having low TC, HDL C and high TG. There was an inverse association between increasing inflammatory markers such as ESR and CRP with HDL cholesterol. I have not observed this pattern of lipids associated with disease activity in my cross-sectional study. However, others studying Indian RA patients have demonstrated that reduction in inflammation after treatment initiation is associated with a rise in HDL-Chol concentration (Hadda V., 2007, Ghosh et al., 2009). Whilst this is possible confounded by DMARD treatment effects it does highlight the importance of optimising control of disease activity in RA. It could be that with better suppression of disease activity that CV risk modification will improve, leading to improved CV outcomes for the RA patient.

This work has highlighted a need for new studies, comparing low, moderate and high DAS groups. To my knowledge the high triglycerides association with low/moderate DAS is a novel finding, which has not been documented in literature. Further studies with fasting lipids are needed to address this finding. It would be worthwhile to study triglyceride levels in prospective studies.

Chapter 8 - Effect of leflunomide on cardiovascular risk in rheumatoid arthritis

In this chapter the effect of leflunomide on CV risk factors in patients with active RA is studied. The prevalence of CV risk factors and composite CHD risk score for the prediction for a CHD event in the next 10 years are calculated before and after starting leflunomide.

8.1 Introduction

Medication used to treat rheumatoid arthritis (RA) may potentially influence the development of associated cardiovascular disease (CVD) in a number of ways. Drugs commonly used in treatment of RA are non steroidal anti inflammatory drugs (NDAIDS), glucocorticosteroids, traditional disease modifying anti rheumatic drugs (DMARDS) and biologic response modifying drugs. NSAIDS are known to be associated with increase in blood pressure (Armstrong and Malone, 2003). Data regarding the use of steroids is controversial; some reports suggest that steroids may adversely affect CVD by increasing body weight, adversely affecting lipid profile, insulin resistance and inducing diabetes (Bartoloni et al., 2011). A literature review has demonstrated a weak association of low dose steroids and CV risk factors but a trend for increase in CV events (Adeline Ruyssen-Witranda, 2011). However the association between steroids and CV events was mostly dose dependent with a higher risk of CV events associated with doses in excess of 10 mg per day The EULAR working group recommendations on management of systemic glucocorticosteroid therapy in rheumatic

diseases advises using low dose steroids (7-10 mg/day) for a short duration and tapering off gradually (Gorter et al., 2010). Use of methotrexate has been associated with a 70% reduction in CV related mortality compared to other DMARDs (Choi et al., 2002). Hydroxychloroquine is associated with an improvement in glucose and insulin sensitivity in patients with lupus and RA and reduces the risk of developing diabetes in association with RA (Androniki Bili 2011). In addition, hydroxychloroquine use has been shown to reduce deleterious effects of glucocorticoids on the lipid profile (Wallace DJ, 1994, Penn SK, 2010). The effects of sulphasalazine on the lipid profile are unclear, with some studies reporting beneficial effects on cardiovascular risk that may be attributed to reduction in inflammation (van Halm et al., 2006) and others the reverse. Sulphasalazine may exert cardioprotective effects by decreasing platelet reactivity (MacMullan P.A. , 2008).

Some observational studies have demonstrated reduced CVD events in RA patients treated with disease modifying anti-rheumatic drugs (DMARDs) (Suissa S 2006, Choi HK 2002,). However, Solomon et al reported an increased risk of CV events in RA patients who received leflunomide (Solomon DH 2006). It was reported that leflunomide may adversely affect the CV risk by increasing blood pressure (Rozman et al., 2002). Little is known about the effect of this DMARD on cardiovascular risk in RA. Hypertension is a recognised side effect of leflunomide. It seems that leflunomide may cause worsening of existing hypertension as well as development of new cases hypertension (Rozman et al., 2002) . A significant rise in BP was reported in up to 10.6% of patients receiving 25 mg leflunomide in a US phase II study of this drug

(Mladenovic V 1995) and newly detected hypertension was observed in nearly 4% of RA patients in a European study (Smolen JS 1999). The mechanisms underlying the rise in BP mediated by leflunomide are not clear. Some studies demonstrated a modest rise in resting heart rate 4-6 weeks after starting this drug, suggesting that the rise in BP may reflect a drug-induced increase in sympathomimetic drive (Rozman B 2002)

The effects of leflunomide on lipids are controversial. Leflunomide was associated with decreased disease activity and a significant increase in total cholesterol and HDL cholesterol. No significant change in the atherogenic index was observed (B. Targońska-Stępniak, 2008). However, another small study reported a progressive deleterious effect of leflunomide on lipid profile (Prokopowitsch AS, 2002); there is also a report of life threatening hypertriglyceridaemia (F. Laborde, 2004). Further studies are needed to explore the effects of this drug on the lipid profile.

Studies on the safety profile of leflunomide have suggested that gastro intestinal disturbance in the form of increased bowel movement, dyspepsia, abdominal pain and weight loss are seen in patients using this drug (Strand V, 1999, Alcorn et al., 2009). Other side effects described include allergic skin rash, alopecia, hypertension and increased liver enzymes (Strand V, 1999, Rozman et al., 2002)(Strand V 1999, Rozman B et al 2002, (E.N. van Roon, 2004). The prevalence of side effects of this drug may be comparable to other DMARDs, but they persist longer, as more than 98% of the drug is bound to plasma protein and has a longer half life than other DMARDs. A recent review article comparing the efficacy and safety of leflunomide and methotrexate as

monotherapy or in combination with biologics has suggested close monitoring of LFT when patients are on this drug. It is possible that leflunomide may increase cardiovascular risk through effects on raising blood pressure (BP). However reduction in inflammatory disease burden may counteract this and reduce cardiovascular risk.

There have been few studies exploring the effect of leflunomide in Asian Indian RA patients. Leflunomide use was associated with an incidence rate of new hypertension of 0.9% in an established RA cohort based in Hyderabad (Rao URK, 2004). In comparison, a multicentre study assessing safety and efficacy of leflunomide in Indian patients reported that, whilst 25% of participants had adverse drug reactions, there was no mention of hypertension as an adverse event (Agarwal SK, 2002). This may be especially notable since a loading dose of leflunomide 100 mg per day for three days was used is these studies. Therefore it is possible that the increased dose in the initial days may be responsible for the new onset hypertension and 25% adverse effects.

Various studies have demonstrated that loading doses of leflunomide did not show extra clinical benefit, but rather a higher rate of adverse reactions (Maddison, 2005, Kremer et al., 2004). Leflunomide use has also been reported to lower blood glucose, which was attributed to a reduction in body weight (Young Hee Rho, 2009). There are no significant data on other traditional CV risk factors and the use of leflunomide.

Leflunomide is a pro-drug that is metabolised in the liver to its active metabolite (teriflunomide) by cytochrome P450. It reduces cell proliferation in activated

lymphocytes, such as those found in patients with RA, by inhibiting dihydroortate dehydrogenase (an enzyme involved in pyrimidine synthesis). Leflunomide is said to improve vascular function by reducing sub endothelial migration of peripheral blood mononuclear cells, inhibiting nuclear factor kappa B signal pathway associated with pro inflammatory and pro atherosclerotic phenomenon in the endothelial cells (Feng H, 2005) and impairment of antigen presenting dendritic cells (Piercarlo Minoretti, 2007). This drug is an effective DMARD in RA with an anti-inflammatory effect and the ability to reduce progression of rheumatoid disease comparable to methotrexate. Whilst clinical effects of leflunomide can commence within a couple of weeks, it may take some months before maximal benefit is achieved(Bożena Targońska-Stępniak, 2008).

Leflunomide is widely used in the treatment of RA as it has proved to be an effective DMARD therapy. However, the drug is costly when compared to other traditional DMARDs. Therefore in India, where patients are responsible for the cost of their drug therapy, it is often reserved for those whose disease is not well controlled by methotrexate, and is usually used in combination with other DMARDS. The monthly cost of leflunomide at the 10mg/day dose is £20/month, rising to £40/month with the 20mg/day dose. This higher dose of leflunomide is too expensive for many RA patients seen in the rheumatology clinic in Hyderabad. Therefore, a routine practice at our clinic is to use 10mg of leflunomide /day in combination with methotrexate therapy or with other DMARDS in the small number of patients who cannot tolerate methotrexate. As studies have suggested that higher dose leflunomide may influence CV risk, and in

particular cause a rise in BP, I was keen to identify whether similar effects would be observed at lower dose in a South Asian Indian cohort of RA patients.

8.2 Aim

The primary aim of this study was to explore whether the introduction of 10mg/day of leflunomide to treat active RA leads to a significant increase in blood pressure and cardiovascular risk.

Secondary aims were to explore whether leflunomide use was associated with modification of lipids, body mass index or fasting blood glucose.

8.3 Methods

Adult RA patients fulfilling ACR criteria (Chapter 1) with inadequate response to existing DMARDS, able to afford the drug and willing to participate between July 2007 and June 2008 were included. All patients had significant disease activity (DAS 28 > 3.2) despite adequate dose of other DMARDs. The study was approved by Sri Deepti Rheumatology Centre ethics committee and all patients gave their written consent to participate. Patients with known CVD, on lipid lowering drugs and those with deformities causing difficulty in anthropometric measurement were excluded.

A full history and examination, as detailed in Chapter 4, were carried out. The assessments were repeated after instituting leflunomide treatment.

8.4 CVD risk assessments

Blood pressure was measured using a Diamond regular (IS3390) sphygmomanometer at baseline, after sitting for fifteen minutes, and repeated twice after ten minutes intervals. The mean of 3 readings was calculated. Fasting blood glucose and a lipid screen including total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were measured. LDL cholesterol was calculated using Friedwald's formula. Patient height and weight were recorded and BMI was calculated. In addition waist:hip ratio was calculated from waist and hip measurements. Patient smoking history was recorded. A 28 joint count, global assessment of disease and ESR were used to calculate DAS28. Health assessment questionnaire was administered. These evaluations were repeated after four month of leflunomide therapy.

The 10 year percentage risk of a coronary heart disease (CHD) event was calculated using the Joint British Societies CHD risk calculator (Durrington 1997). This calculates a 10 year CHD risk based on systolic and diastolic BP separately. A ten year CHD risk of 10% or more was defined as elevated CHD risk. These measures were then repeated 4 months after leflunomide 10mg daily was started. Twenty milligram (mg) per day was not used as it was costlier and may increase the possibility of toxicity.

8.5 Drug therapy

Current medication including regular NSAID, DMARDs and glucocorticosteroid use were noted. Participants on prednisolone used < 7.5 mg per day. Patients were initiated on leflunomide 10mg per day without loading doses. Any change in requirement for

NSAIDs or glucocorticoids was recorded. In all situations leflunomide was added in combination to other DMARDs in order to step up DMARD therapy. Nine patients were on etanercept which was withdrawn as leflunomide was started. On improvement in joint pain the patients were allowed to reduce or stop the dose of glucocorticosteroid and NSAIDs.

8.6 Analysis

The study was powered based on an anticipated 10% increase in BP with leflunomide treatment. Using this estimation of effect size, power of 0.9 and alpha of 0.05 a sample size of 40 patients was required.

Baseline pre leflunomide measures of BP and CV risk factors were compared with values recorded after 4 months of leflunomide treatment. Significance testing using paired T-test for normally distributed variables and Wilcoxon's signrank test for non-parametric data. Chi squared test was used to compare categorical variables pre and post leflunomide treatment.

8.7 Results

A cohort of 40 RA patients was identified. The patient and disease characteristics are summarised in Table 8.1. The mean age of the cohort was 48.5 years and 93 % were female. Patients had established RA with median disease duration of 5.5 years. This cohort of patients did not include any smokers. All were established on DMARDs and the baseline treatment is summarised in table 8.2.

Methotrexate (mtx) was used by 95% of the cohort. Patients were advised to continue with their DMARD therapy during the period of this study. The only change to rheumatic drug therapy was withdrawal of etanercept around eight weeks after adding leflunomide. All patients had active RA at the time of starting leflunomide. The median DAS 28 score was 7.1, reflecting high RA disease activity. At the baseline assessment all but one patient was using regular NSAIDs for symptom control and 77% were also using oral glucocorticoids. All patients were on methotrexate 10-15 mg/week, the median dose being 12.5mg/week. Prednisolone was used in a physiological dose of less than 7.5 mg/day.

Table 8.1 Baseline disease characteristics of the cohort

Variables	Description	RA Cohort n=40	
Age (yrs)	mean (SD)	48.5	10.3
Gender Female n (%)	n (%)	37	92.5
Vegetarian n (%)	n (%)	17	42.2
Duration of RA (years)	med [IQR]	5.5	3, 11.5
Rheumatoid factor positive n (%)	n (%)	39	97.3
DAS 28	med [IQR]	7.1	5.7, 7.6
ESR	med [IQR]	85	58, 115
CRP	med [IQR]	48	48, 48
Global health VAS	med [IQR]	75	50, 100
Swollen joint count	med [IQR]	6	3, 10
Tender joint count	med [IQR]	13	6, 18
HAQ score	med [IQR]	1.75	1.50, 2.24
BMI Kgs/m^2	mean (SD)	25.8	0.7
History of DM	n (%)	9	22
History of hypertension	n (%)	11	27.5

Abbreviations:- (med) – Median, (SD) - Standard deviation, [IQR] - Inter quartile range.

Table 8.2 Baseline anti-rheumatic therapy

Medication	n	%
Methotrexate	38	95.0
Sulphasalazine	1	2.3
Hydroxychloroquine	3	7.7
Glucocorticoids	30	76.9
NSAIDs	39	97.5
Etanercept	9	22.5

8.7.1 Response to leflunomide treatment

Table 8.3 demonstrates the observed change in disease variables for the cohort. There was evidence of significant improvements in disease activity with evidence of reduction in swollen and tender joint counts ($p<0.001$). The inflammatory markers reduced with treatment and the DAS 28 dropped from a median of 7.1 to 4.9 after 4 months of leflunomide treatment($p<0.001$). The median HAQ score also dropped significantly from 1.75 to 0.92 demonstrating a marked reduction in level of disability ($p<0.001$). Of interest, the proportion of patients requiring: 1) NSAID treatment reduced from 98% to 78%, and 2) steroid treatment dropped from 77% to 43% ($p=0.003$).

Table 8.3 Change in disease variables with leflunomide treatment

Variables	Description	Pre-leflunomide treatment		Post-leflunomide treatment		statistical test used	p value
ESR	med [IQR]	85	58, 115	43	32.5, 66.5	Wilcoxon's signrank	p<0.001
CRP	med [IQR]	48	48, 48	24	24, 48	Wilcoxon's signrank	p<0.001
Global health VAS	med [IQR]	75	50, 100	30	20, 50	Wilcoxon's signrank	p<0.001
Swollen joint count	med [IQR]	6	3, 10	2	1, 3	Wilcoxon's signrank	p<0.001
Tender joint count	med [IQR]	13	6, 18	5	2, 7	Wilcoxon's signrank	p<0.001
DAS 28	med [IQR]	7.1	5.7, 7.6	4.9	4.1, 5.4	Wilcoxon's signrank	p<0.001
HAQ score	med [IQR]	1.75	1.50, 2.24	0.92	0.69, 1.29	Wilcoxon's signrank	p<0.001
NSAID use	n (%)	39	97.5	31	77.5	chi squared	p=0.007
Steroid use	n (%)	30	76.9	17	42.5	chi squared	p=0.003

The cardiovascular risk assessments are shown in table 8.4. At baseline, prior to starting leflunomide, 33% of patients had elevated systolic BP. Of this group, only 5 were known to have hypertension and no modification of antihypertensive therapy was instituted.

Table 8.4 Comparing CVD risk factors pre and post leflunomide treatment.

Variables	Description	Pre-leflunomide treatment		Post-leflunomide treatment		statistical test used	pvalue
Systolic BP (mmHg)	mean (SD)	128.0	2.4	127.0	2.0	paired t-test	p=0.79
High systolic BP (≥140 mmHg)	n (%)	13	33	9	23	paired t-test	p=0.31
Diastolic BP (mmHg)	mean (SD)	84.1	1.2	84.5	1.2	paired t test	p=0.79
High diastolic BP (≥90 mmHg)	n (%)	20	50	18	45	chi squared	p=0.65
Pulse pressure systolic-diastolic	mean (SD)	43.3	2.0	42.5	1.6	paired t test	p=0.65
BMI Kgs/m^2	mean (SD)	25.8	0.7	25.8	0.6	paired t-test	P=0.75
Waist:Hip ratio	mean (SD)	0.89	0.01	0.89	0.01	paired t-test	p=0.18
FBS	mean (SD)	93.2	2.7	91.0	2.1	paired t-test	p=0.40
Total Cholesterol	mean (SD)	180	4.48	178	5.0	paired t test	p=0.68
HDL Cholesterol	mean (SD)	46.5	0.9	48.2	1.00, 52	paired t-test	p=0.08
Low HDL	n (%)	5	12.5	1	2.5	chi squared	p=0.09
Triglyceride	mean (SD)	128.4	9.8	120.7	8.0	paired t-test	p=0.47
T- Chol:HDL Chol ratio	mean (SD)	3.9	0.64	3.7	0.53	paired t-test	p=0.04
Composite CHD risk scores							
CHD risk score † (systolic BP)	mean (SD)	5.3	0.8	4.8	0.8	paired t-test	p=0.47
High CHD risk score†† (systolic BP)	n (%)	8	20	7	17.5	chi squared	p=0.77
CHD risk score * (diastolic BP)	mean (SD)	5.9	0.9	5.4	0.8	paired t-test	p=0.08
High CHD risk score** (diastolic BP)	n (%)	10	25	6	15	chi squared	p=0.26

SD standard deviation, 95% CI Confidence interval, DAS28: 28 joint Disease activity score, ESR: Erythrocyte Sedimentation Rate.

† (% risk of CHD event over 10 years, based on systolic BP)

†† (≥10% risk of cvd event over 10 years based on systolic BP)

* (% risk of CHD event over 10 years, based on diastolic BP)

** (≥10% risk of cvd event over 10 years based on diastolic BP)

No significant differences were noted in either systolic or diastolic BP before and after starting leflunomide. It was noted that the mean BP remained the same on leflunomide therapy. However, the proportion with elevated systolic BP (systolic BP ≥140 mm of

Hg) fell from 13 (33%) to 9 (23%) after leflunomide was started. As leflunomide therapy is often avoided in the presence of hypertension, this is an interesting observation.

At baseline it was observed that 13 (32.5%) of patients had elevated systolic BP. When the group was stratified by baseline systolic BP, those with baseline systolic BP less than 140 mmHg (normotensive patients), had a statistically significant mean increase in systolic BP of 4mmHg (SD 9.3 mmHg) (paired t test p=0.02); whilst those with elevated systolic BP (systolic BP $\geq$140) at baseline had a statistically significant reduction in systolic BP of 9.2mmHg (SD 12.6) after starting leflunomide therapy (paired t test =0.01). No anti-hypertensive medication was added during the period of this study.

In both the systolic hypertension subgroup and the normotensive subgroup, leflunomide use was associated with a 23% reduction in NSAIDS use. The prevalence of steroid use was also reduced by 40% in both the systolic and normotensive subgroups. No significant difference in reduction in DAS28 scores were observed when the normotensive and systolic hypertensive subgroups were compared.

There was a non-significant trend for improvement in nearly all the individual components of the CHD risk score. However, the composite CHD risk score did not significantly change after leflunomide was started. Whilst total cholesterol level and triglyceride level were lower after starting leflunomide, this was not a significant

difference. There was a trend for HDL cholesterol level to increase and total cholesterol: HDL C ratio was observed to reduce with leflunomide treatment (p=0.04). A significant reduction in T- Chol: HDL ratio was also observed, with a drop from 3.9 to 3.7. However, the size of this reduction was very small and is unlikely to be of clinical significance.

8.8 Discussion

This small study of the effect of leflunomide on cardiovascular risk has not demonstrated any significant increase in either systolic or diastolic BP with this treatment. If anything, the blood pressure was observed to fall after leflunomide was added and the magnitude of BP reduction was largest in those patients with elevated BP at the baseline assessment. The encouraging results of a fall in systolic BP of 9.2 mm of Hg in patients with elevated blood pressure are important. As blood pressure is one of the components of CV risk assessment, even a small reduction in blood pressure (10-12 mm of Hg) substantially reduces CV risk.

The reason for the paradoxical reduction in BP is likely to be explained by the reduction in RA disease activity and a reduced requirement for NSAIDs and glucocorticoids after leflunomide was started. It was interesting to note that the fall in BP was only observed in the subgroup with hypertension at baseline and there was a very modest rise in the systolic BP observed in the baseline normotensive patients with leflunomide treatment..

When the prevalence of NSAID and glucocorticosteroid use was explored, no difference was observed in the reduced requirements for these drugs in either subgroup. This suggests that the change in BP is not simply due to a change in requirement for NSAIDs and glucocorticoids. However, we were unable to record the reduction in dose of steroids in the patients who continued steroid treatment. This study was not adequately powered to explore this in more detail.

Another possible explanation for a fall in BP might be due to the reduction in anxiety in RA patients as they become accustomed to the study assessments, or possibly as a consequence of reduced pain associated with reduced disease activity. However, as response to leflunomide did not differ between those who, at baseline, were normotensive and those with elevated systolic BP, this would not explain the paradoxical changes in BP observed in these two subgroups.

The modest mean rise in systolic BP of 4 mmHg observed in the baseline normotensive patients is of a magnitude similar to that seen in previous clinical trials of leflunomide. An earlier phase three study observed a mean increase in systolic BP of 2.2 mm of Hg and a diastolic BP of 1.9 mm of Hg (Strand V, 1999). Hypertension was reported in 3.7% of patients in another phase two study (Smolen et al., 1999).

Another interesting observation was the slight but significant reduction in the total cholesterol to HDL-Chol ratio. This was largely driven by an increase in the concentration of HDL and is likely to reflect the improvement in the inflammatory

disease burden rather than any effect of leflunomide on lipid metabolism. However, leflunomide is metabolized to the active drug by cytochrome P450 1A2 in the liver. Up regulation of this enzyme may have a beneficial effect on the lipid profile. Studies have demonstrated that drug induced elevation of liver cytochrome P450 is associated with higher levels of apolipoprotein AI (apo AI) and HDL cholesterol (HDL-C) as well as reduced LDL cholesterol (LDL-C) levels in plasma. Therefore, it is possible through the liver metabolism of leflunomide, that there may be a beneficial effect on lipid profile through induction of cytochrome P450. My finding is in contrast to a previous study in thirty established RA patients observed before and three months after starting the drug which observed that, though there was an insignificant trend for an increase in TC and triglyceride, the atherogenic index (T-Chol:HDL-Chol) remained constant and leflunomide failed to demonstrate an effect lipid profile in RA patients (van Halm 2003). Patients in that study were older than our study participants, had a longer duration of disease (9.8years) and a lower proportion of females than my cohort and were already on multiple DMARDs, leflunomide was the fourth DMARD added. The observed effects may not be directly attributed to leflunomide alone because background medications for RA were multiple. The disease activity of RA and the use of steroids and NSAIDs have not been recorded. However this study did not explore the effects of leflunomide on blood pressure nor its effect on other CV risk factors. We have observed an improvement in the atherogenic index.

Earlier studies have shown that dyslipidaemia is associated with systemic inflammation in RA (Park TB 2002). What was interesting in this study was the fact that the HDL increased, despite reduction in the proportion of patients using glucocorticosteroid

medications. Previous studies have demonstrated that use of glucocorticoids tends to cause a rise in HDL levels, but it is not clear whether this is due to the effects of inflammation reduction or due to an effect of the glucocorticoids (Boers M 2002), which alter carbohydrate and lipid metabolism (Hansel B 2010). The increase in HDL cholesterol may possibly be due to the direct hepatic effects of leflunomide. However this needs further investigation.

A limitation of this study was that it was observational and no placebo treatment group was examined. Both patients and researchers conducting the assessments were aware of treatments prescribed. It is possible that this lack of blinding to treatment may have influenced the study results. However it is unlikely that this would have changed the individual CV risk factors especially the lipid profiles. It would have been useful to conduct this study using a double blind cross over trial design. This would have overcome problems with bias. However, as the current study relied on participants being responsible for the cost of their drug treatment it was not ethical or practical to conduct the study using placebo treatment period

A recent study from the Asia Pacific region (New Zealand) in 90 patients on leflunomide looking at the long term survival characteristics and side effect profile of the drug reported gastrointestinal side effects to be the most common. The patients were followed for 6.5 years and rather interestingly the investigators did not observe any CV side effects of leflunomide. The investigators could not consistently record the starting dose of the drug, the patients were older than in my cohort and there was no information

about disease activity (Jagoda, 2011). Another study in Pakistani patients comparing the effect of leflunomide monotherapy and in combination with methotrexate for 24 weeks did not mention CV side effects of the drug. The age of those patients was similar to our cohort and all patients had active disease. However, there was no consistency in either the use of loading dose or maintenance dose of the drug (10 – 20 mg /day was used) (Nighat M. Ahmad, 2011). An observational study in Indians observed only 5 out of 230 patients developed hypertension with leflunomide use (Arvind Chopra 2008). Whereas Rao et al (Rao URK, 2004) observed 0.9% of 548 patients on leflunomide for six months had high blood pressure during follow up. These two studies used a loading dose of leflunomide. With the results from Asia Pacific populations it would be interesting to know if there is a true difference in safety of leflunomide in different geographical and ethnic backgrounds. It would be interesting to note the CV effects of leflunomide in Asia Pacific countries.

Leflunomide had been in general use for more than a decade, yet there is not much published about its effect on CV risk. My findings are interesting and need to be addressed in further studies that are powered to investigate the effect of leflunomide on individual CV risk factors. It would be intriguing to explore the direct effect of this drug, over a longer period of follow up, in larger number of patients with a stable dose of steroids and NSAIDs.

The primary aim of this study was to explore if leflunomide increases blood pressure. I have found that the drug does not increase blood pressure - on the contrary, there appears to be a fall in blood pressure. In addition, I did not find evidence for increased cardiovascular risk with use of leflunomide in active RA. The possibility that leflunomide may lead to improvements in RA-associated dyslipidaemia is an attractive hypothesis, but warrants further study in a larger group of patients, allowing for adjustment for confounding effects of reduced inflammation and glucocorticosteroid use.

Finally, the fact that this was an observational prospective study and conducted in a routine clinical setting, carries a greater applicability for these results to be relevant to the general RA population, compared to randomised clinical trials. This may be of special value for South Asian Indian RA patients, who have increased CV risk factors and limited choice of the use of DMARDs, especially biological response modifiers, due to their prohibitive cost.

Chapter 9 - The influence of etanercept treatment on cardiovascular risk in active rheumatoid arthritis

This chapter explores whether a short course of treatment with the anti-tumour necrosis factor alpha (anti-TNF) drug, etanercept, is associated with a change in the CV risk profile of patients with active RA. The patients' CV risk profiles were evaluated at baseline, and at 3 and 6 months after the anti TNF drug was withdrawn.

9.1 Introduction

Rheumatoid arthritis is associated with increased mortality and morbidity which may be attributed to RA specific factors such as disease activity related dyslipidaemia, vascular inflammation, medicines used to treat RA or increased levels of circulating pro inflammatory cytokines like tumour necrosis factor alpha. There are reports that use of anti TNF treatment reduces the CVD event rate in RA patients who respond to treatment (Dixon and Symmons, 2007). Therefore, this suggests that anti-TNF treatment may influence CV risk in RA. However, in the study by Dixon et al, CVD event rates were only reduced in the subgroup of RA patients who demonstrated moderate to good EULAR response to anti-TNF therapy, and were not reduced in those who were non responders. If CVD events were only reduced in responders this suggests that the reduction in CVD events may reflect reduction in inflammation rather than a beneficial effect of the anti TNF drug on CV risk factors.

Many studies have explored the effect of anti TNF treatments on markers of vascular function in RA. Endothelial function is found to improve with anti TNF treatment (Hurlimann et al., 2002). However, this beneficial effect was found to be transient in another study with endothelial function returning to pre treatment levels after one month of therapy. However, in this same study the authors have supported long term use of the drugs to reduce CV complications based on a reduced rate of atherosclerosis mediated by endothelial function (Gonzalez-Juanatey et al., 2004).

Long term (2yrs) treatment with etanercept has demonstrated a reduction of carotid IMT in RA patients (Ferrante et al., 2009). A meta-analysis of the effect of anti TNF alpha therapy has demonstrated that there is reduced risk of all CV events in observational cohorts (Barnabe et al., 2011). However, Suissa et al failed to observe any reduction in CVD event rates in anti-TNF treated RA patients compared to patients treated with traditional DMARD therapies (Suissa et al., 2006).

The effect of anti TNF treatment on lipid profiles in RA is controversial. Some studies have not observed any effect of the treatment on the lipid profile. (Soubrier et al., 2008). However, several studies have reported an increase in total cholesterol. In a study by Seriolo et al (Seriolo et al., 2006) anti TNF treatment was given to 34 active RA patients and the lipid profile was measured at baseline and 16 and 24 weeks and it was found that treatment was associated with an increase in T-Chol and HDL cholesterol but the atherogenic index remained the same. The same findings were also confirmed in a review article (Schimmel EK, 2009). Anti TNF treatments have found to increase HDL

cholesterol (Popa et al., 2005, Spanakis et al., 2006). We know from other studies that inflammation influences the lipid profile in RA. Several studies have demonstrated a rise in total cholesterol with suppression of systemic inflammation (Boyer et al., 2011, Kitas, 1997)(Situnake). As the studies exploring the influence of anti TNF on lipid profiles were conducted in different RA populations with varying levels of disease activity, it is difficult to know whether the lipid modification reflects a direct effect of the drug or the effects of reduced inflammation.

In addition, metabolic syndrome and insulin resistance may be modified by anti-TNF therapy (Popa et al., 2007). In type 2 diabetic patients use of anti TNF therapy has been reported to reduce the level of insulin resistance (Rosenvinge A, 2007). A Spanish study on 27 RA patients has reported improvement in insulin resistance 2 hours after infliximab infusion (Gonzalez-Gay et al., 2006).

Previous studies have mentioned the effect on CV risk factors while the patients were continuing anti TNF treatments. No study in the literature addresses whether the effect is sustained after the withdrawal of the drug. The effects of anti TNF treatment on lipids are controversial and the information in South Asian Indian patients treated with anti TNF treatments with respect to traditional CV risk is scanty.

In the UK currently 5 TNF treatments are available 1) infliximab a chimeric monoclonal antibody given as an intravenous infusion in a dose of 3-5 mg / kg body weight, 2) Etanercept a recombinant fusion protein given as a 25 mg subcutaneous injection twice

a week, 3) Adalimumab a fully humanized antibody given as 40 mg subcutaneous injection every other week 4) Certolizumab pegol is given as a 400 mg subcutaneous injection on week 2 and 4 followed by 200 mg every other week , and the most recently licensed 5) Golimumab is a synthetic protein given as a 50 mg per month subcutaneous injection. However in India only Infliximab and Etanercept are available.

In contrast to western countries, RA patients in India are mostly self funded and are responsible for the cost of their treatment. As biologic response modifiers are costly, patients cannot afford to use them for indefinite periods. Hence, biologic response modifiers are used for a short duration usually about three to four months to try and induce remission / or improve disease activity which is later maintained by non biologic traditional DMARDS. Indian patients use this expensive treatment to try and optimize their disease control infrequently and often this investment is made prior to an important family or social event. Examples of these situations that we often observe in the rheumatology practice at the Sri Deepti Rheumatology Centre include planned travel to attend their children's wedding or to go abroad to help their children especially during pregnancy and delivery. Before such occasions patients request use of anti-TNF in order to optimize better disease control. In this situation if the patient or their family can afford it arrangements are made to initiate a short course of biologic response modifiers. The cost of this course of anti TNF treatment is around 2,600 GBP. Though this is not a licensed use of the drug, nor it is evidence based, this is the usual clinical practice. There are instances where patients use etanercept single dose as and when required at times similar to a steroid injection. This use was not included in this study. As our clinic

is in an outpatient setting the most commonly used biologic drug is etanercept due to the ease of administration.

9.2 Aim

The aim of this study was to explore whether 4 months use of etanercept influences CV risk factors in patients with active rheumatoid arthritis after etanercept is withdrawn.

Secondary aims were to explore whether any long-term effect on CV risk is observed 6 months after etanercept is withdrawn.

9.3 Methods

This prospective observational study was conducted in patients who were exposed to a short course of anti TNF therapy, with etanercept, as part of their ongoing rheumatology treatment.

Patients were invited to take part in the study if they had active RA (defined as a DAS28>5.1), despite treatment with methotrexate or methotrexate in combination with other DMARDs like leflunomide, sulphasalazine or hydroxychloroquine. As patients were responsible for the costs of all medication, this subgroup of patients was not representative of the rest of the RA cohort described in chapter 4. They represented a more affluent subgroup of patients, as the high cost of 4 months of etanercept was beyond the socioeconomic capabilities of most of the patient group studied in chapter 5. DMARDs and prednisolone were at a stable dose for three months prior to starting etanercept. The treatment and assessment protocol is described in Figure 9.1.

The ethics committee Sri Deepti Rheumatology Centre approved the study and all participants gave written consent to participate.

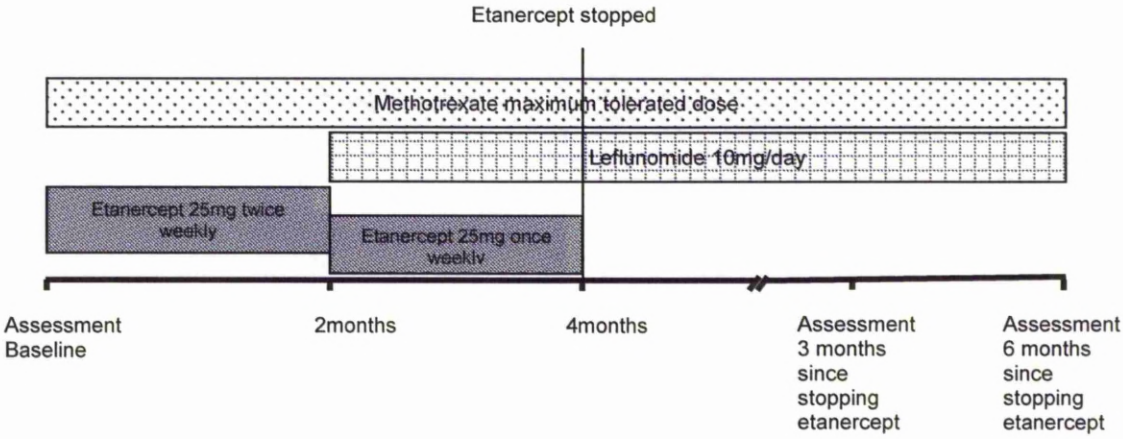
9.4 Assessments

Before the anti-TNF treatment was started, baseline assessments of RA disease, its treatment and CV risk measurements were recorded. These assessments are described in chapter 4. The assessments were repeated three and six months after etanercept treatment had been withdrawn. Concomitant medication history was taken at each evaluation. The patients included in this study have active disease as defined by a DAS 28 of > 5.1.

9.5 Anti-TNF treatment

All eligible patients used etanercept 25 mg subcutaneously twice a week for two months then the dose was reduced to 25 mg / week for another two months then the drug was withdrawn. The patients were allowed to adjust the dose and stop NSAIDs and glucocorticosteroid if their joint disease was controlled. DMARDs were allowed to be altered if needed. At the time of tapering the etanercept dose leflunomide at a dose of 10 mg / day was added to the drug therapy.

Figure 9.1 Treatment and assessment protocol



9.6 Analysis

The CV risk factor distributions and prevalence of elevated risk factors are described at baseline and 3 months after etanercept. The difference in risk factor distributions at these 2 time points were assessed using paired t tests for normally distributed data, Wilcoxon's matched pair signrank test for non parametric data and chi squared for binomial data.

The analysis was then repeated in the subgroup that provided 6 months follow up data after etanercept was stopped.

9.7 Results

9.7.1 General details

Forty one active rheumatoid arthritis patients with inadequate response to traditional DMARDS who could afford drug costs of etanercept were included. The cohort of patients included 36 females and five males. All forty one patients underwent a repeat analysis 3 months after stopping etanercept treatment and 25 of the original subgroup underwent a further assessment 6 months after etanercept therapy was withdrawn (Table 9.1).

Table 9.1 Assessments before and after 3 and 6 months treatment with etanercept

	All	Females	Males
	n	n	n
Pre etanercept treatment	41	36	5
3 months after etanercept treatment	41	36	5
6 months after etanercept treatment	25	22	3

9.7.2 CV risk factors and RA disease variables pre and post etanercept treatment

9.7.2.1 RA disease variables before and 3 months post etanercept treatment

At the baseline assessment this cohort of RA patients had a median RA disease duration of 5 years. However, the cohort was quite heterogeneous with a range of disease durations spreading between 6 months and 26 years. Rheumatoid factor was positive in 40 patients (97.6%). All patients had active disease as shown by the high median DAS28 scores of 7.7. The 28 tender and swollen joint counts were elevated and global disease visual analogue scale (VAS) was 100. The median ESR was 103 mm/ hr.

After patients had been treated with etanercept, the assessment 3 months after etanercept was withdrawn revealed a significant reduction in the DAS 28 score from 7.73 to 4.64 ($p<0.001$). The results in table 9.2 reveal that this reduction in DAS28 score was due to reduced 28 joint counts and a marked reduction in global health and ESR.

Table 9.2 RA disease variables before and 3 months after etanercept treatment

Parameter	Description	Pre etanercept n=41		3 m post etanercept n=41		p value
Duration RA (yrs)	median [IQR]	5	3, 11	5	3, 11	NS
RF +ve	n (%)	40	97.6	40	97.6	NS
SJC	median [IQR]	12	8, 15	2	0, 4	p<0.001
TJC	median [IQR]	18	14, 24	4	2, 6	p<0.001
Global dis VAS	median [IQR]	100	80, 100	30	20, 40	p<0.001
ESR	median [IQR]	103	85, 125	42	30, 56	p<0.001
DAS28	median [IQR]	7.73	7.08,8.28	4.64	3.64,5.39	p<0.001

IQR- inter quartile range, n-number, RF+ve- rheumatoid factor positive, SJC- swollen joint count, TJC- tender joint count, Global dis VAS- global disease visual analogue scale, ESR- erythrocyte sedimentation rate, DAS 28- disease activity score of 28 joints.

The concomitant medicines used by the cohort are given in Table 9.3. At baseline all of the patients reported use of NSAIDs and steroid use was reported by 38 (92.7%). All but one patient reported current use of Methotrexate (97.6%). The dose of methotrexate ranged between 10-15 mg / week and prednisolone was used in a physiological dose of < 7.5 mg /day. Leflunomide use was reported in 34.2% of patients whereas hydroxychloroquine and sulphasalazine were both infrequently used. Combinations of DMARD drugs were used by 41% of the cohort at baseline.

Three months after etanercept was withdrawn, NSAID use by the cohort was reduced significantly from 100% to 73.2%) ($p<0.001$). In addition, use of any steroid medications was also significantly reduced from 92.7% to 43.9%. Whilst all patients were started on Leflunomide as the dose of etanercept was reduced, not all patients remained on this medication. At the 3 month assessment only 22 (53.7%) were still taking leflunomide in addition to their other DMARD therapies.

Table 9. 3 Concomitant medicines before and 3 months after etanercept treatment

Parameter	Description	Pre etanercept		3 m post etanercept		p value
NSAIDs	n (%)	41	100	30	73.2	P<0.001
Steroids	n (%)	38	92.7	18	43.9	P<0.001
Etanercept	n (%)	0	0	0	0	NS
Methotrexate	n (%)	40	97.6	40	97.6	NS
Leflunomide	n (%)	14	34.2	22	53.7	p=0.08
Hydroxychloroquine	n (%)	4	9.8	7	17.1	NS
Sulphasalazine	n (%)	1	2.4	2	4.9	NS

NS: Not significant p values after significance testing with Chi squared test.

9.7.2.2 General demographics in patients before and 3 months after etanercept treatment

The baseline median age of the patients was 48.9 years. Thirty six out of 41 patients (87.8%) were females. Vegetarian diet was reported by 16 (39%). None of the patients were smokers. The most frequently observed co morbidity was DM (29.3%) followed by HTN (12.2%). None of the patients had co morbid CVD. Patients with known CVD on treatment were excluded.

9.7.2.3 Blood pressure before and 3 months after etanercept treatment

The median diastolic blood pressure remained constant during the course of the study. The baseline systolic blood pressure was 130 mm of Hg and dropped to 120 mm of Hg 3 months after etanercept see Table 9.4.

High systolic BP (>140 mm of Hg) was observed in 29.3% of patients. Three months after etanercept treatment there was a significant reduction in the number of patients having a high systolic BP (p=0.01). Whilst the number of patients with elevated diastolic BP dropped from 12 to 8 this difference did not reach statistical significance.

Table 9.4 Blood pressure before and 3 months after etanercept treatment

Parameter	Description	Pre etanercept		3 m post etanercept		†Chi2	p value
Systolic BP	median [IQR]	130	120, 140	120	110, 130		0.03
Diastolic BP	median [IQR]	80	80, 90	80	80, 80		NS
Elevated systolic BP							
Systolic BP ≥140	n(%)	12	29.3	3	7.3	6.6	0.01
Diastolic BP ≥ 90	n(%)	13	31.7	8	19.5	1.60	0.21

BP-blood pressure, NS: not significant pvalues after paired t-test, or Chisquared testing

9.7.2.4 Anthropometric measurements

The median height of the cohort was 157 centimetres and the median weight was 65 kilograms. The median BMI was 25.2 and median waist: hip ratio was 0.9. There was no significant change in the BMI or waist: hip ratios after etanercept treatment. The proportions with high waist: hip ratios and BMI in the overweight/obese categories did not show any change during the course of the study.

9.7.2.5 Fasting blood glucose and lipid parameters

The median fasting blood glucose was 87mg / dl and there was no significant change during the course of the study. None of the patients had elevated blood glucose greater than 126 mg/dl. The median baseline total cholesterol was 164 mg / dl and was constant 3 months after exposure to etanercept. Median baseline HDL cholesterol was 48 mg/dl and triglyceride was 126 mg/ dl. Though the total cholesterol remained same there was a trend for a slight reduction in triglycerides (126 mg/dl to 118mg/ dl) and HDL cholesterol (48 mg/dl to 47 mg/ dl) levels, 3 months after etanercept treatment was withdrawn see Table 9.5.

Table 9.5 Fasting blood glucose and lipid parameters before and 3 months after etanercept treatment

Parameter	Description	Pre etanercept		3 m post etanercept		†Chi2	p value
T- Chol	median [IQR]	164	151, 188	164	152, 186		0.92
HDL-Chol	median [IQR]	48	44, 51	47	44, 50		0.72
TG	median [IQR]	126	91, 171	118	98, 152		0.51
FBS	median [IQR]	87	81, 98	85	75, 92		0.28
Elevated lipids and fasting blood glucose							
T-Chol >200	n(%)	8	19.5	5	12.2	0.82	0.36
HDL-Chol<40	n(%)	1	2.4	2	4.9	0.35	0.55
T-Chol:HDL ratio >4.5	n(%)	6	14.6	3	7.3	1.12	0.28
TG >150	n(%)	15	36.6	11	26.8	0.90	0.34
FBS >100	n(%)	8	19.5	6	14.6	0.34	0.56
FBS in DM range >126	n(%)	0	0	0	0	-	-

Wilcoxon's Ranksum test used to explore for significant differences between median lipid values

† Chi squared used to compare proportion with elevated risk factor after 3 months with pre treatment value

9.7.2.6 Composite ten year risk of CHD event by JBS

The calculated median ten year predicted risk of a CHD event by joint British societies CHD risk score calculator at baseline was 3.3% based on systolic BP and 3.9% when calculated using diastolic BP. There was an insignificant trend for an increase in the CHD risk score 3 months after etanercept treatment. There was an insignificant trend for an initial reduction of CV risk factors three months after therapy see Table 9.6.

Reduction in the number of patients with a high (>15%) CHD risk score was seen 3 months after treatment with etanercept (7.3% to 0%).

Table 9.6 Composite ten year risk score of CHD event

Parameter	Description	Pre etanercept		3 m post etanercept		†Chi2	p value
CHD risk (Systolic)	median [IQR]	3.3	1.3, 6.9	3.8	1.5, 5.7	0.91	NS
CHD risk (diastolic)	median [IQR]	3.9	1.1, 7.2	4.5	1.5, 6.9	0.92	NS
Elevated 10 year CHD risk							
*10 year CHD risk >10%(systolic)	n(%)	6	14.6	4	9.8	0.46	p=0.50
*10 year CHD risk >15% (systolic)	n(%)	3	7.3	0	0	3.11	p=0.08
*10 yearCHD risk >10% (diastolic)	n(%)	8	19	5	12.2	0.82	p=0.36
*10 year CHD risk >15% (diastolic)	n(%)	3	7.3	2	4.9	0.21	p=0.64

† Chi squared used to compare proportion with elevated risk factor after 3 months with pre treatment value

NS:Not significant result

9.7.3 Influence on CV risk factors and RA disease variables six months after etanercept treatment

In a sub group of twenty five patients from the cohort of forty one patients started on etanercept a repeat analysis was done six months after the drug withdrawal.

9.7.3.1 RA disease variables before and 6 months after etanercept treatment

The baseline disease variables in the sub group were as follows RA disease duration was 7 years (see Table 9.7). The disease duration in this sub group was longer than the original cohort (5 yrs). RF positive disease was seen in 96%. Compared to baseline values a significant sustained effect of etanercept on disease activity was observed six months after etanercept was withdrawn. All disease activity parameters showed a statistically significant improvement ($p<0.001$). The follow-up of the 25 patients demonstrated that there was a significant reduction in DAS28 which was maintained, 6 months after etanercept treatment (7.87 – 4.47).

Table 9.7 RA disease variables before and 6 months after etanercept treatment

Parameter	Description	Pre etanercept n= 25		6 m post etanercept n=25		p value
Duration RA (yrs)	median [IQR]	7	3, 13	7	3, 13	NS
RF +ve	n (%)	24	96	24	96	NS
SJC	median [IQR]	14	7, 16	1	0, 4	p<0.001
TJC	median [IQR]	19	16, 26	4	1, 6	p<0.001
Global dis VAS	median [IQR]	100	75, 100	30	20, 30	p<0.001
ESR	median [IQR]	102	80, 125	44	28, 52	p<0.001
DAS28	median [IQR]	7.87	7.08, 8.37	4.47	2.99,5.04	p<0.001

NSAID use was reported by 100% of the patients before etanercept was started six months after the drug was withdrawn there was significant reduction in the requirement (56% ($p<0.001$)).

Requirement of steroids dropped from 96% to 32% ($p<0.001$). The dose of methotrexate was between 10-15 mg / week and prednisolone was used in a physiological dose of < 7.5 mg /day. A slightly higher proportion of this subgroup

remained on leflunomide than that seen in the whole cohort observed at 3 months. Leflunomide use rose from 28% pre etanercept to 72% six months after etanercept see Table 9.8.

Table 9.8 Concomitant medicines before and 6 months after etanercept treatment

Parameter	Description	Pre etanercept		6 m post etanercept		p value
NSAIDs	n (%)	25	100.0	14	56.0	p=<0.001
Steroids	n (%)	24	96	8	32.0	p=<0.001
Etanercept	n (%)	0	0	0	0	NS
Methotrexate	n (%)	24	100.0	24	100.0	NS
Leflunomide	n (%)	7	28.0	18	72.0	p=0.002
Hydroxychloroquine	n (%)	2	8	3	12	NS
Sulphasalazine	n (%)	0	0	0	0	NS

NS: Not significant p value

9.7.3.2 General demographics in patients before and 6 months after etanercept treatment

The mean age of this sub group of patients was 51.3 years and increased to 52.3 years. Eighty eight percent of the group was females forty percent were vegetarian. None of the participants were smokers. Co morbid hypertension was more frequently seen in 36% of patients and diabetes in 20% see Table 9.9.

Table 9.9 Demographics, co morbidities and blood pressure before and 6 months after etanercept treatment

Parameter	Description	Pre etanercept n= 25		6 m post etanercept n=25		p value
Demographics						
Age	Mean (SD)	51.3	(9.6)	52.3	9.6	NS
Female gender	n(%)	22	88.0	22	88.0	NS
Vegetarian	n(%)	10	40.0	10	40.0	NS
Smoker	n(%)	0		0		NS
Co morbidities						
HTN	n(%)	9	36.0	9	36.0	NS
DM	n(%)	5	20.0	5	20.0	NS
CVD	n(%)	0	0	0	0	NS

NS: Not significant p value

9.7.3.3 Blood pressure before and 6 months after etanercept treatment

No change in blood pressure was observed before and 6 months after etanercept treatment. High systolic blood pressure > 140 mm of Hg was seen in 29.3 percent of patients at baseline and 24% six months after etanercept was withdrawn see Table 9.10.

Table 9.10 Blood pressure before and 6 months after etanercept treatment

Parameter	Description	Pre etanercept		6 m post etanercept		‡Chi2	p value
Systolic BP	median [IQR]	130	120, 140	130	120, 130		NS
Diastolic BP	median [IQR]	80	80, 90	80	80, 90		NS
Elevated systolic BP							
Systolic BP ≥140		7	29.3	6	24.0	0.1	p=0.74
Diastolic BP ≥ 90		7	28.0	12	48.0	2.1	p=0.15

‡ Chi squared used to compare proportion with elevated risk factor after 6 months with pre treatment value (in the 25 patients that had 6 month assessments)

NS: Not significant p value

9.7.3.4 Anthropometric measurements

The median height of the group was 157 centimetres. Baseline weight was 63 Kg, BMI was 24.8 and waist : hip ratio was 0.89 see Table 9.11. Six months after etanercept was withdrawn there was no significant change in the anthropometric measurements though there was an insignificant trend for mild increase in weight, BMI and waist measurements.

Table 9.11 Anthropometric measurements before and 6 months after etanercept treatment

Parameter	Description	Pre etanercept		*6 m post etanercept		‡Chi2	p value
Height	median [IQR]	157	153, 161	157	149, 163		NS*
Weight	median [IQR]	63	57, 71	64	58, 74		NS
BMI	median [IQR]	24.8	22.8, 28.3	26.0	22.2,28.7		NS
Waist cm	median [IQR]	93	86, 95	94	86, 98		NS
Hip cm	median [IQR]	103.5	96, 108	103	96, 106		NS
Waist:Hip Ratio	median [IQR]	0.89	0.86, 0.95	0.91	0.86, 0.94		NS
Elevated waist:hip ratio and BMI							
High Waist:Hip ratio	n (%)	5	20.0	3	12.0	0.6	0.44
BMI>25	n (%)	12	48.0	14	56.0	0.32	0.57

‡ Chi squared used to compare proportion with elevated risk factor after 6 months with pre treatment value (in the 25 patients that had 6 month assessments)

NS: Not significant p value

9.7.4.5 Fasting blood glucose and lipid parameters

Baseline median total cholesterol was 173 mg/ dl, HDL cholesterol was 48mg/dl and triglyceride was126 and fasting blood glucose was 89 mg/dl. There was an insignificant trend for increase in total cholesterol and HDL cholesterol. Triglyceride level was reduced six months after etanercept was withdrawn (126 mg / dl to 115 mg / dl). There was no change in the fasting blood glucose levels see Table 9.12

Low HDL cholesterol <40mg/dl was not observed in any patient at baseline but after six months of stopping the drug there was a slightly significant increase in the number of patients with a low HDL cholesterol (p=0.07).

Table 9.12 Fasting blood glucose and lipid parameters before and 6 months after etanercept treatment

Parameter	Description	Pre etanercept		6 m post etanercept		‡Chi2	p value
Total Cholesterol Units	median [IQR]	173	159, 196	180	158, 195		0.83
HDL Cholesterol	median [IQR]	48	46, 52	49	43, 52		0.97
Triglycerides	median [IQR]	126	100, 171	115	92, 139		0.22
FBS	median [IQR]	89	81, 98	89	86, 94		0.81
Elevated lipids and fasting blood sugar							
T C >200mg/dl	n (%)	6	24	5	20.0	0.12	0.73
HDLC<40mg/dl	n (%)	0	0	3	12.0	3.19	0.07
TC:HDL ratio >4.5	n (%)	4	16.0	3	12.0	0.17	0.68
TG >150mg/dl	n (%)	8	32.0	6	24.0	0.40	0.53
FBS >100mg/dl	n (%)	6	24	4	16.0	0.50	0.48
FBS in DM range >126 mg/dl	n (%)	0	0	0	0	-	-

‡ Chi squared used to compare proportion with elevated risk factor after 6 months with pre treatment value (in the 25 patients that had 6 month assessments)

NS: Not significant p value

9.7.4.6 Composite ten year risk of CHD event by JBS

The median 10 year CHD risk score for the probality of a CHD event calculated by JBS was 3.5 (systolic) and 3.9 (diastolic). There was an insignificant trend of reduction in elevated CV risk factors. The CHD risk score was same before and 6 month after etanercept was withdrawn see Table 9.13.

Table 9.13 Composite ten year risk score of CHD event

Parameter	Description	Pre etanercept		6 m post etanercept		‡Chi2	p value
CHD risk (Systolic)	median [IQR]	3.5	2.2, 3.5	4.3	2.6, 6.9		0.66
CHD risk (diastolic)	median [IQR]	3.9	2.7, 10.4	5.7	3.3, 9.0		0.69
*10 year CHD risk >10% (systolic)	n (%)	5	20.0	5	20.0	0	1.0
*10 year CHD risk >15% (systolic)	n (%)	3	12.0	2	8.0	0.22	0.63
*10 year CHD risk >10% (diastolic)	n (%)	7	28.0	5	20	0.44	0.51
*10 year CHD risk >15% (diastolic)	n (%)	2	8.0	2	8.0	0.22	0.64

‡ Chi squared used to compare proportion with elevated risk factor after 6 months with pre treatment value (in the 25 patients that had 6 month assessments)

Wilcoxon's sign rank test used to compare median CHD risk scores

In the repeat analysis comparing 6 months after etanercept we see that the association with reduced prevalence of systolic hypertension was lost see Table 9.10. However, the numbers are smaller as fewer patients had 6 month data. The only association that remains significant at 6 months is the reduced exposure to steroids.

9.8 Discussion

This small cohort of RA patients demonstrated a significant reduction in their DAS 28 with a short course of etanercept. The requirement of NSAIDs and steroids was reduced. However there was no significant change in the cardiovascular risk factor profile apart from a modest reduction in systolic BP at the 3 month assessment which was not sustained when the analysis was repeated 6 months after etanercept was withdrawn. It appears from this study that short term use of etanercept does not lead to

sustained improvement in CV risk factors after the drug is withdrawn. Non blinded nature of this study was in accordance with routine clinical practice and was not foreseen to impact the outcome.

There are several possible explanations for this modest improvement in systolic BP after short term exposure to anti-TNF therapy. One explanation might be that as disease activity was improved in the months after etanercept was used this may have lead to less chronic pain. We know from physiological studies that severe pain is associated with a rise in blood pressure although this is more marked in the acute setting with increased sympathetic drive (Chawla PS, 1999). The fact that disease activity was reduced and patients were less dependent on NSAIDs may also have contributed to the modest reduction in BP. We know that NSAID use can lead to a rise in BP through effects on the kidney causing salt and fluid retention. By the 3 month assessment 27 % of the cohort had managed to stop using any NSAIDs and this reduction in NSAID use may have been responsible for the improvement in systolic BP. Unfortunately it was not possible, because of the small cohort size to stratify the group into those dependant on NSAIDs and repeat the analyses. What was interesting was that the increased use of leflunomide during the months following withdrawal of etanercept was not associated with increase in BP. As hypertension is one of the commonly described side effects of leflunomide therapy (Rozman et al., 2002), we have not seen any marked increase in BP with use of this drug at the 10 mg dose in this cohort. This reflects the results presented in chapter 8 section 8.7 the leflunomide chapter where addition of leflunomide was not seen to be associated with any increase in hypertension.

It is rather interesting to note that three months after etanercept there was a moderate but not statistically significant reduction in the number of patients having a high (>15%) CHD risk score but this reduction did not persist 6 months after therapy. It is likely that the reduction in systolic blood pressure resulted in the initial reduction in CHD risk score.

Surprisingly there is a mild increase in number of patients with a low HDL < 40 mg/ dl. The exact reason for this is not known. Anti TNF treatment has been demonstrated to increase HDL cholesterol (Popa C 2005, Spanakis E 2006). However, these studies were carried out on predominantly Caucasian patients and it is possible that dyslipidaemia in Indian RA patients may respond in a different way though, the number of patients having a reduced HDL is small it is worth exploring this finding in studies with larger patient cohorts.

A modest beneficial effect of leflunomide on atherogenic index was seen in the study presented in chapter 8. It is possible that any effect of etanercept on HDL level has been reduced by the concomitant addition of low dose leflunomide in this study. In order to try and separate out the effect of etanercept on lipid profiles, repeating this study in a more controlled environment without the addition of leflunomide would help to explore whether short courses of etanercept have any significant adverse effects on HDL levels in Indian RA patients.

Most of the published literature, reporting a beneficial effect of anti TNF treatment on lipid profile is with prolonged use of anti TNF alpha (Dahlqvist et al., 2006). There are conflicting reports about the effect of anti TNF therapy on lipid profile. Studies reporting a short term effect of the drug have evaluated patients after a short duration of drug use but, those patients were still continuing anti TNF treatment .One study has observed an increase in HDL cholesterol and T-Chol but no change in atherogenic index (Seriolo et al., 2006) another study (Soubrier M, 2008) failed to observe any effect on lipid profile in patients treated with anti TNF agents. However, these studies did not observe the lipid profile after stopping anti TNF treatment to see the sustained benefit. To our knowledge this is the first study looking at the CV risk factors after the anti TNF treatment was withdrawn.

To our knowledge this is also the first study in South Asian Indian RA patients with a biologic response modifier – etanercept looking at the traditional CV risk factors and subjecting the patients to repeat evaluations after stopping etanercept and observing the change in response after the drug was withdrawn. Rather surprisingly there was no significant increase in disease activity even 6 months after stopping the drug. This finding is important in a developing country like India where patients are mostly self funded for their treatment and not many patients can be benefited from the costly treatments even when they have active disease. This approach may not alter the CV risk profile but is effective in disease control as demonstrated in this study. The encouraging finding of a sustained response can motivate rheumatologists of developing countries to give a short course of a biologic to induce remission / reduction in disease activity and

maintain the response by increasing the dose of existing DMARDs or the addition of an additional DMARD like leflunomide. This concept of treatment is not described in literature.

In the western countries where biologic response modifiers are used for an indefinite periods this concept of induction of remission can be used and the cost of treatment can be significantly reduced and the drug can be made available to larger number of patients by cutting the per patient cost of therapy.

With the advent of biosimilar drugs the treatment scenario especially in developing countries may change. The biosimilars reduce the treatment costs significantly. However, it would be a concern as a difference in impurity and breakdown products can have serious health complications. Testing procedures based on a thorough demonstration of comparability of the similar product to an existing approved product are needed (Genazzani et al., 2007). These drugs are referred to as follow on biologics by the FDA and subsequent entry drugs in Canada. The US FDA has been given authority to approve bio similar drugs as per "Patient protection and affordable care act" (March 23, 2010). The European medicines agency has drafted guidelines that may expand the market for biosimilar compounds.

There are a number of limitations with this study. The major limitation was that it was not possible to assess CV risk in patients whilst they were treated with etanercept and before leflunomide was added. This was the original plan for the study but as most

patients "save up" for etanercept exposure to optimize their disease control to help with significant family events; most patients were unable or unwilling to attend the clinic for CV assessments at that time. Also as they would only have had 2 months treatment by that time this short period of drug exposure may not have had sufficient time to lead to any CV risk modification. Therefore the decision was taken to explore whether etanercept was associated with risk factor modification after drug was withdrawn. We were also unable to repeat the analysis six months after etanercept therapy in all patients due to uncontrollable factors. Some of the patients had gone abroad to meet their children and others were not residing in Hyderabad at that time and could not come for a repeat analysis at the 6 month assessment. This was an observational study and no placebo arm was used. However as discussed in chapter 8 page 197, we would not expect this to change laboratory reports like ESR and lipids.

The other major weakness of the study was that large numbers of patients exposed to patients could afford the drug. If this study was to be repeated recruitment of patients from multiple similar rheumatology centres would be a way to increase the cohort size. Studies with larger numbers and longer follow up are needed in South Asian Indian RA patients to demonstrate the effect on traditional CV risk factors and also to support the concept of induction of remission with biologic response modifiers.

Chapter 10 – Discussion

This chapter discusses results obtained from this study as a whole, in the light of present literature. Public health messages, regarding life style modification and the need for treating physicians, rheumatologists and cardiologists to be made aware of the gravity of problem are highlighted. Finally, the potential for future studies in this population to further investigate this are described.

10.1 Main findings of the study

This study, which explored the prevalence of traditional cardiovascular risk factors in South Asian Indian patients, has revealed interesting findings that impact not only on the population studied, but also a wider scale. I observed a dramatic increase in the prevalence of all traditional CV risk factors in this cohort; with a fourfold increased composite 10year CHD risk score of a CV event. The fact that the RA patients in my cohort were younger than the participants in most other studies, the increased traditional CV risk factors and composite CHD risk scores is rather alarming and has major public health implications. In contrast to other studies, smoking was rarely described by either cases or controls. The number of smokers overall was too small to detect an association with RA.

The median BMI in the two groups was in the overweight /obese range (25 kg/m2). Even though the cases and controls displayed an increased prevalence of obesity, a high waist to hip ratio was strongly associated with having RA. Co-morbidities such as hypertension, diabetes and hypothyroidism also had an association with a diagnosis of

RA, with hypertension the most frequently observed co-morbidity. The diagnosis of RA was associated with dyslipidaemia, in the form of elevated total cholesterol, high triglycerides and low HDL. All of the factors constituting the metabolic syndrome also had an association with being a case of RA with almost half of the participants in the RA cohort meeting the diagnostic criteria for metabolic syndrome.

Traditional CV risk factors were not found to have a strong relation with disease activity. Furthermore, the finding of low/moderate disease activity being associated with high triglycerides was not expected and needs further exploration. Despite the fact that majority of the study participants were females, the significantly increased 10 year risk of a CHD event in RA cases highlights an urgent need for mortality studies in this population of South Asian Indian patients and a greater public health awareness.

In contrast to common the general perception in the past, leflunomide was not associated with increase in blood pressure in my cohort. Indeed, this drug appeared to reduce blood pressure in hypertensive individuals – an observation that needs further exploration in a bigger cohort with longer follow up.

Finally, whilst a short course of the biologic response modifier etanercept did not have a sustained effect on traditional CV risk factors, the sustained effect on disease activity is encouraging and may set a trend for inducing reduction of RA disease burden. Although this study was not powered to explore the long term effect of etanercept on DAS 28 my finding needs to be further explored.

10.2 Individual CV risk factors

When CV risk factors were examined individually, a strong association with being a case of RA was detected. There was a trend for elevated blood pressure to be more frequently seen in patients with RA. A high diastolic blood pressure of >95 mm Hg was associated with RA. My cohort had particularly active disease, with patients taking NSAIDSs and glucocorticosteroids. Although it is known that these agents are associated with hypertension, I am not aware of reports of these drugs mediating a selective rise in diastolic blood pressure. The stress related to having RA and its associated adverse impact on life is also not likely to have a selective effect on diastolic blood pressure. This finding of diastolic hypertension being associated with RA therefore needs to be addressed in future studies.

When compared to controls, RA was strongly associated with elevated fasting blood glucose and co morbid type 2 DM. It is possible that the effect of active disease in reducing mobility may have resulted in glucose intolerance. It is also possible that rheumatoid cachexia, which results in increased fat mass and reduced lean muscle mass, with increased abdominal girth and increased waist hip ratio may have played a role. Whilst I did not measure body composition formally in this study, I did record waist and hip measurements and observed that the waist to hip ratio was higher in RA cases, despite similar BMI between cases and controls – suggesting an unfavourable body composition in the RA cases.

The observation that dyslipidaemia, in the form of high total cholesterol and low HDL cholesterol, resulting in an unfavourable atherogenic index, was intriguing. As the RA cases had active disease, I would have expected them to have low total cholesterol and low HDL cholesterol, as tends to be observed in inflammatory states. The finding of an unfavourable atherogenic index in the context of RA was particularly interesting, because the background South Asian population is known to have increased prevalence of CVD. The active inflammatory disease in RA should was expected to result in lower levels of triglycerides - however, I observed that hypertriglyceridaemia was associated with being a case of RA. Indian patients with RA often report a vegetarian diet. The effect of diet on triglycerides in RA was not explored. This should be considered in further studies, together with the potential effects of individual drug therapies in a controlled manner.

I found that RA patients displayed an increased composite CHD risk score four times that of controls. This observation is especially alarming. Male gender, age and smoking are the important constituents of CHD risk estimation - our RA cohort had a majority of female participants who were younger and reported infrequent smoking, yet had an increased CHD risk. Longer term studies could investigate the effects of this on CV events and mortality. However, the data I have generated suggests that public health measures should be set in place now, to protect this high-risk population for the future.

All the risk factors that cluster in metabolic syndrome were frequently reported in cases and controls, though the frequency was much higher in patients with RA. The strongest

association with being a case of RA was metabolic syndrome. The increased prevalence of metabolic syndrome reported in South Asian Indians, compounded with a diagnosis of RA and therefore further magnifying CV risk needs to be better understood and acted upon. Potential mechanisms that might underlie this should also be investigated in further studies that might uncover novel strategies to target this therapeutically.

Disease activity was not found to be associated with traditional CV risk factors. At first sight this may appear to be counter intuitive. It was also surprising to note that low/ moderate disease activity was associated with high triglyceride levels. Increased triglyceride levels are known to be associated with active RA. My cohort was skewed to highly active disease, rendering comparisons with lower disease activity less practical. My finding of elevated triglyceride in low/ moderate disease activity should be explored further in a larger cohort that contains a higher proportion of patients with less severe disease activity and, ideally, patients in remission.

Though the addition of leflunomide and etanercept was not blinded, we did not anticipate any impact on study outcome nor any bias in patient examination. As the patients were responsible for the cost of their treatment and we do not expect the lack of blinding to affect the CV risk factors. Hence, the possibility of a placebo response is ruled out.

It was reassuring, if not somewhat surprising, to find that leflunomide was not associated with hypertension. Indeed, the hypertensive group displayed reduction in

systolic BP when on leflunomide. This is an important finding, as blood pressure is an extremely important constituent of CHD risk estimation and a reduction in blood pressure results in reduction of CHD risk score. This finding may reduce current apprehensions with the perceived association between leflunomide with hypertension and, importantly, provide a cheaper option to treat refractory active RA in developing countries. I also observed a modest improvement in the atherogenic index with the use of leflunomide. However, the number of patients in the study was too small to draw firm conclusions and was not powered to investigate these aspects. Further studies with larger number of participants having disease for a longer duration are needed to address this finding of reduction of blood pressure in hypertensive individuals and improvement of atherogenic index. CHD risk prevention scores should be applied to these participants and the effect of leflunomide on the 10 year composite CHD risk score addressed.

Whilst my observation that just a short course of the TNF inhibitor, etanercept, produced a sustained reduction in disease activity was encouraging, the fact that this did not reveal a sustained effect on traditional CV risk factors was not expected. This may be explained by a number of potential factors. I have already discussed that elevation of disease activity was not associated with a rise in traditional CV risk factors. It is possible that the duration of exposure to etanercept may have been too short to detect significant changes in the parameters that I measured. In addition, my patient cohort was recruited from a tertiary care centre, a potentially skewed population. As patients in India are self-funded, there is a possibility that those with reduced disease activity may visit the clinic less frequently. I also was not able to record the details of the patients

who refused participation – potentially missing those patients who were happy with their mildly active disease and therefore not wanting further evaluation. I could not compare the active RA patients with those with a low DAS 28 as all the participants in the RA cohort had active disease. I was also unable to collect all information from participants on etanercept, as this was not possible in the routine clinical setting of this study. Few Indian patients can afford biologic response modifiers, due to their prohibitively high cost. These drugs tend to be reserved for use at the time of an important family or social event and not all patients could make the repeat clinic visit at the required time.

10.3 The study findings in light of published literature

The strong association between RA and metabolic syndrome found in my study population has been reported in literature (Karvounaris et al., 2007, Elisa Gremese 2011, Sidiropoulos et al., 2008) and the association also observed in individuals without a history of CVD (Crowson et al., 2011). The prevalence of metabolic syndrome was increased in RA compared to osteoarthritis and the normal population (Dessein et al., 2002). Chronic inflammation is frequently associated with metabolic syndrome (Julie P Sutherland, 2004). A meta-analysis has reported that metabolic syndrome is associated with a two fold increase in the risk of CVD, CV mortality, myocardial infarction and stroke (Mottillo S, 2010). In addition to the increased background of inflammation and increased risk of CVD, the chronic inflammation in RA may result in further magnification of the risk. Patients with metabolic syndrome have an increased risk of

having moderate to severe RA and disease activity was found to correlate with the presence of the number of metabolic syndrome parameters (Karvounaris et al., 2007).

South Asian Indians are known to have clustering of CV risk factors which constitute the metabolic syndrome (Misra and Khurana, 2011). Raised inflammatory markers were also observed in South Asian Indians (Indulekha et al., 2011). A recent study in urban Indians without inflammatory arthritis has observed a prevalence of metabolic syndrome in females as high as 58% (Das, 2011). The fact that having RA was associated with an 80% increased risk of having metabolic syndrome is a matter of concern, as this group has an increased risk of developing type 2 diabetes and may have a high risk of future CV events. Contrary to the assumption that use of treatments for RA may reduce the factors constituting metabolic syndrome, it was found that RA patients with metabolic syndrome had a lower possibility to achieve good response to treatment (Elisa Gremese 2011). The patients in my cohort taking leflunomide and etanercept did not experience a change in their features of metabolic syndrome. However this finding needs to be explored in future studies. At this juncture it is difficult to establish a relation between RA, metabolic syndrome and the treatments used to treat RA.

I used the NCEP ATP III criteria to assess metabolic syndrome, using a high cut off. A lower cut off has been proposed for different ethnic populations. The cut off for BMI and waist:hip ratio is also lower, but their predictive value in identifying T2 DM and CVD compared to earlier cut offs has been debated (Misra and Vikram, 2008).

The DMARD, hydroxychloroquine, is associated with a decreased risk of diabetes and improved glycaemic control (Bili et al., 2011). Earlier studies have also demonstrated improvement of lipid profile with the use of this drug (Munro R, 1997). It may be worth studying the effects of hydroxychloroquine on the features of metabolic syndrome in this high-risk population in the future.

An increased prevalence of diastolic hypertension in South Asians compared to Caucasians has been documented in an earlier study (Ajjan et al., 2007). The RA cohort in this study had increased frequency of diastolic hypertension when compared to controls. This is a matter of concern and needs to be addressed urgently.

Type 2 diabetes was found to be more prevalent in RA as per an earlier meta-analysis addressing traditional CVD risk factors (Boyer et al., 2011). South Asians Indians are known to the highest prevalence of diabetes in the world (Gupta R, 2007) and diabetes is known to occur a decade earlier than Caucasians and other Asians (Mather HM, 1998). Though there was no difference in BMI between the two cohorts, a high waist:hip ratio was associated with being a case of RA. This could be an explanation for the increased prevalence of diabetes found in the RA cohort. In the context of RA, the twenty times increased prevalence of elevated fasting blood sugar is a serious matter and requires immediate attention.

The typical pattern of dyslipidaemia with high total cholesterol, high triglycerides, high atherogenic index and low total cholesterol is also an important finding. It reported in the literature that active disease is associated with low total cholesterol, low HDL cholesterol (White et al., 2006) and low triglycerides (Iannello S, 2003). A study from north India demonstrated a negative association between disease activity, total cholesterol and disease modification with 3 months of DMARDs, with modest elevation of total cholesterol and no signification association with HDL cholesterol and triglycerides. (Hadda V., 2007). In contrast, I observed a modest improvement of atherogenic index with three months use of leflunomide. These observations need to be studied further.

The increased prevalence of traditional CV risk factors has resulted in increased composite CHD risk score of a probability of a CHD event in 10 years to be strongly associated with being a case of RA. The CHD risk score was high in RA cases, both by Framingham risk score and JBS; but a higher CHD risk score (>15%) was observed with the JBS scoring system. Most of the studies in South Asian Indian RA patients have used the Framingham risk score for prediction of a CHD event. JBS may also be used in future studies. The relative sensitivity of these scores in predicting a CHD event and choice of optimal score for the future can be identified by following these two cohorts over time to address the occurrence of events and mortality.

The EULAR guidelines suggest that RA should be treated as a condition with high risk of CVD (Peters et al., 2010) - the increased risk being attributed to traditional CV risk

factors and RA disease activity. Aggressive treatment of disease activity is rightly recommended, but in a country like India, where the patient is responsible for the cost of the treatment, the choice of medicines is considerably limited. The majority of Indian RA patients cannot afford biologics. The advent of biosimilars with lower cost may hopefully change the picture. The modest improvement of the atherogenic index and no increase in blood pressure with leflunomide is an encouraging finding in our scenario. The EULAR guidelines suggest an annual CV risk assessment that can be performed less frequently in patients who do not have a high risk. The suggestion of a 1.5 multiplication factor in calculating CV risk for RA patients is also made. There is already a suggestion of further multiplication of CV risk in ethnic populations. My study suggests that, in the context of a South Indian population, this should be considered urgently, with additional data to inform this potentially gained from further follow up of my cohort. Pending development of better local guidelines, it is even more important that EULAR guidelines should be followed.

RA is known to occur ten years earlier in Indians (Chandrasekaran and Radhakrishna, 1995). Diabetes occurs ten years earlier and CVD is also seen at a younger age (Enas et al., 1992). My RA cohort had active disease without particularly long disease duration. As the RA patients were younger compared to most of the published literature, the effect of the increased prevalence of CV risk factors should be explored in a future mortality study. It would also be interesting to know if RA is a risk factor for CVD in this population.

10.4 Public health message and avenues for future research

My work has identified the urgent need for a fresh focus on RA and new public health messages for India. In light of my findings of increased prevalence of traditional CV risk factors in RA, life style modification measures in patients with RA are needed. Most of the elevated risk factors like diabetes, hypertension, dyslipidaemia and high waist:hip ratio, all clustering to increase the prevalence of metabolic syndrome can potentially be successfully improved by lifestyle modification with for example patients being especially encouraged to increase mobility and exercise (Turesson and Matteson, 2007). The successful implementation of this will, however, be a considerable challenge. It was rather surprising to know the response of patients when they were made aware of their elevated/high composite 10 year CHD risk score. Some patients were concerned about their increased risk of a CHD event, some were angry that another problem is anticipated which would further increase their expenditure. Few patients responded by saying that since they were not productive and were a burden to their family members it was good that they would die. Hence patient education is of outmost importance. The patients should be encouraged to have health insurance which is not very commonly observed in individuals living India. I am not aware of a CV event in the RA cases or controls when this study data was analysed.

Physicians, rheumatologists and cardiologists should be made aware of the gravity of the problem and be particularly proactive in identifying and treating CV risk factors in RA. Co morbidities should be identified and treated. Blood pressure measurements should be performed at every clinic visit and patients with elevated blood pressure and

those with existing hypertension should be advised to adhere to antihypertensive medication and monitor their blood pressure regularly.

Blood glucose monitoring should also be done frequently. Anthropometric measurements of the patients should be taken periodically and evaluation of criteria for metabolic syndrome should become routine. An annual lipid profile should be performed and interventions made as indicated. After conducting this study my colleagues and I in Hyderabad have changed our practice and, for example, have started checking lipid profiles in our patients.

The unexpected finding of sustained reduction of disease activity with just a short course of the biologic response modifier etanercept is reassuring that this approach is effective from a disease suppression angle. This approach can be potentially applied in developing countries, where active RA patients are unable to afford expensive drugs for more than short periods of a time at best. The advent of biosimilar drugs may help drive the costs of such treatments down, particularly benefitting active RA patients in countries such as.

Lifestyle modification, in the form of increased activity and diet modification should be repeatedly emphasised at regular intervals. This should become a routine practice at times such as giving a fresh prescription for medicines. The landmark INTERHEART case control study, looking at 15,000 patients in 52 countries with first presentation of myocardial infarction, has suggested that traditional CV risk factors should not be

neglected in South Asians. High waist:hip ratio was found to be related to population attributable risk to an even greater than that associated with smoking (Salim Yusuf and John Varigos, 2004, Joshi P, 2007).

Aggressive treatment of RA to reduce the inflammatory burden should be advocated. There is a case to promote more extensive use of the traditional DMARD hydroxychloroquine, due to its beneficial effects on lipids and blood glucose. Dyslipidaemia should be treated. In addition to treating dyslipidaemia, statins are known have anti-inflammatory effects and to be associated with reduced CV events in individuals with elevated CRP levels in the absence of dyslipidaemia (Ridker, 2002). The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) placebo controlled trial, evaluating the effect of statins in reducing CV events and strokes in persons with normal cholesterol, demonstrated a reduction in the levels of hs CRP and LDL in patients on statins. There was also a modest reduction in the risk of CV events and stroke (Ridker PM, 2008). Other drugs known to have a beneficial effect on the CV system are angiotensin converting enzyme inhibitors and folic acid.

The need for addressing CV risk factors in RA by increasing awareness of the need for aggressive intervention as in diabetes and established CVD (Kumar and Armstrong, 2008) is pressing. As the CVD risk in RA is similar to that observed in diabetes, RA should be considered as an individual risk factor for CVD (Peters et al., 2009) in its own right.

10.5 Urgent need for studies in South Asian Indian RA patients

India is the second most populated country in the world with a population 1.21 billion (as per 2011 census). The Indian population amounts to 17.31% of the world population. One out of six persons in the world is from India. The world health organisation (WHO) has reported that cardiovascular disease is rising in Indians at an alarming speed and, by the year 2020, CVD will be the largest cause of disability and death in Indians (WHO 2005). The prevalence of rheumatoid arthritis in Indians is 0.75%, which equates to more than 9 million patients with RA - yet there is paucity of data for so many aspects of RA in India. I have created the largest RA case control database in the country. My study has confirmed the increased prevalence of traditional CV risk factors in South Asian Indians and a strong association of RA with metabolic syndrome. Whether RA truly is an independent risk factor for CVD in this population should be investigated by following these patients, observing the CVD event rate and exploring if this is affected by CV risk factors.

If the composite CHD risk prediction scores are valid in these patients, I anticipate that this increased CHD risk will correlate with an increased CHD event rate in the RA cases as these patients are followed up. As yet, no CVD morbidity or mortality studies have been conducted in RA cohorts in India. Possible barriers to this type of study include difficulty in obtaining accurate cause-specific mortality data because of a lack of population-based mortality registers in this country. However, if assumptions are made, based on the CHD risk scores predicting absolute risk of CHD events, I estimate that in the 90 RA patients with risk in excess of 15% some 14 patients would be expected to

have a significant CHD event. If the same approach were applied to the controls, only 7 would be expected to have a significant event. This would equate to a 2 fold increase in CVD events described in the RA cardiovascular literature (Wolfe and Michaud, 2008) (van Halm et al., 2009) (Solomon et al., 2003). This, together with the fact that there is an overall increased prevalence of CV risk in the general population of India, suggests that my work has been particularly timely and may lead to fundamental changes in consideration of CV risk in South Asian Indian RA patients for the future.

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